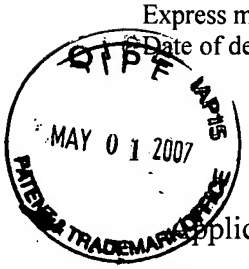
05-02-07

DAC

10/083,245
Petition to revive
Express mail label no.: EQ 789470687 US
Date of deposit: May 1, 2007



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Darrow et al.	Docket No.:	37737-003
Serial Number:	10/083,245	Examiners:	Truong, T. (old); Moore, S.
Filing Date:	February 25, 2002	Art Unit:	1624
Title:	Certain alkylene diamine-substituted pyrazolo[1,5-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines		

Petition for Revival of Unintentionally Abandoned Application under 37 C.F.R. §1.137(b)

1. Revival of the above application for reasons of unintentional abandonment is respectfully requested pursuant to 37 C.F.R. §1.137(b). Applicants assert, for the reasons described below, that the entire delay in submitting the required reply (Amendment and Response) from the due date for the reply until the filing of a grantable petition was unintentional.

2. An Amendment and Response with Terminal Disclaimer was submitted December 9, 2005 to a final Office action dated October 12, 2005 (a copy of the Amendment and Response is attached hereto as Appendix **A**). The Amendment and Response was received by the U.S. Patent and Trademark Office (the Office) and date stamped December 9, 2005 (a copy of the return postcard stamped by the Office is attached hereto as Appendix **B**). The Amendment and Response was timely received by the Office, within two months of mailing of the final Office action, and therefore Applicants expected an Advisory Action according to MPEP §706.07(f) and §714.13. The Terminal Disclaimer was accepted and posted on Public Pair. See Appendix **C** attached hereto which is a print-out of the Terminal Disclaimer Approval form used by the Office.

3. Telephonic conferences initiated by Examiner Truong were held on January 19, 2006 and January 20, 2006 in which she indicated to Applicants that she would allow the claims. In the course of the conferences, Applicants called to the Examiner's attention numerous technical errors introduced into the application as published. Applicants inquired as to whether they might submit a mark-up of the published application (attached hereto as Appendix **D**) to restore the application as filed, and as the Examiner agreed, submitted via facsimile a communication that

05/03/2007 FMETEKI1 00000028 10083245
01 FC:1453 1500.00 OP

was made of record in Public Pair as of January 31, 2006. Following submission of a timely Amendment and Response to the outstanding Office action and telephonic conferences initiated by the Examiner, Applicants waited for a Notice of Allowance or an Advisory Action. Applicants sincerely believed that the Examiner required time to consider errors introduced into the published application.

4. However, Applicants received a Notice of Abandonment mailed June 28, 2006. Applicants on July 5, 2006 submitted a Petition to Withdraw the Holding of Abandonment, which Petition was dismissed in a Decision mailed October 12, 2006. Applicants then submitted on October 20, 2006 a Request for Reconsideration of Petition, which Petition was dismissed in a Decision mailed April 27, 2007. No undue delay has been incurred from receipt of correspondence mailed from the Office and Applicants' replies; rather, zealous efforts have consistently been undertaken on behalf of this application.

5. No newly prepared reply is required with this Petition, as the reply (Amendment and Response) to the final Office action mailed October 12, 2005 was timely submitted on December 9, 2005, within two months. See Appendix **E** which is a print-out of the transaction history of this case on Public Pair, showing that Applicants' reply is of record.

6. A Terminal Disclaimer dedicating to the public the terminal part of any patent granted thereon from the date of the notice of abandonment (June 28, 2006) to the filing of this petition (May 1, 2007) is attach hereto as Appendix **F**.

7. For the above reasons, Applicants respectfully request that the Petition for Revival of Unintentionally Abandoned Application be granted, and that a Notice of Allowance or a non-final Office action be mailed to Applicants' representative. Applicants enclose check no. 36077 in the amount of $1,500.00 for the fee due under 37 C.F.R. §1.17(m). Please charge any additional fee or credit any excess to Deposit Account No. 503344, Ref. No. 37737-003.

Respectfully submitted,

Sonia K. Guterman

Sonia K. Guterman, Reg. No. 44,729
Attorney for Applicants
Lawson & Weitzen, LLP
88 Black Falcon Ave., Suite 345
Boston, Massachusetts 02210
Tel: (617) 439-4990
Fax: (617) 439-3987
Customer Number 48425

Dated: May 1, 2007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Darrow et al.	Docket No.:	37737-003
Serial Number:	10/083,245	Examiner:	Truong, T.
Filing Date:	February 25, 2002	Art Unit:	1625
Title:	Certain alkylene diamine-substituted pyrazolo[1,5-A]-1,3,5-triazines		

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Terminal Disclaimer

The co-owners, Pfizer, Inc. and Neurogen Corporation, of the instant application assigned by the inventors James Darrow, Stephane De Lombaert, Charles Blum, Jennifer Tran, Mark Giangiordano, David Griffith, and Philip Carpino,

hereby disclaim, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§154 to 156 and 173, as presently shortened by any terminal disclaimer, of patent number 6,372,743 B1 and patent number 6,476,038 B1. The co-owners hereby agree that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patents are commonly owned, such that the patents are exclusively licensed to Pfizer, Inc. and co-owned by assignees Pfizer, Inc. and Neurogen Corporation. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

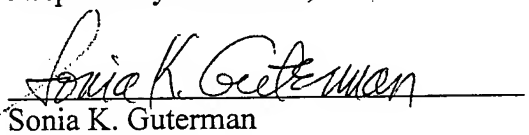
In making the above disclaimer, the co-owners do not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §§154 to 156 and 173 of the prior application or any patent granted on the prior application, as presently shortened by any terminal disclaimer, in the event that either any patent granted on the prior application later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent

jurisdiction, is statutorily disclaimed in whole or terminally disclaimed in whole or terminally disclaimed under 37 C.F.R. §1.321, has all claims cancelled by reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of their full statutory term as presently shortened by any terminal disclaimer.

I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or patent issued thereon.

The undersigned Applicant's representative files this Terminal Disclaimer under 37 C.F.R. §1.34(a). Check number 30833 in the amount of $130.00 for the terminal disclaimer fee under 37 C.F.R. § 1.20(d) is included. Applicants believe no additional fee is due, however the Commissioner is hereby authorized to charge any additional fees or make any credits to Deposit Account No. 503344, Ref. No. 37737-003.

Respectfully submitted,



Sonia K. Guterman
Registration No. 44,729
Lawson & Weitzen, LLP
88 Black Falcon Ave., Suite 345
Boston, Massachusetts 02210-2481
Tel: (617) 439-4990
Fax: (617) 439-3987
Customer Number 48425

Date: December 9, 2005

Appendix **A**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Darrow et al.	Docket No.:	37737-003
Serial Number:	10/083,245	Examiner:	Truong, T.
Filing Date:	February 25, 2002	Art Unit:	1625
Title:	Certain alkylene diamine-substituted pyrazolo[1,5-A]-1,3,5-triazines		

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Amendment and Response

This paper is in response to an Office Action mailed October 12, 2005 from the United States Patent and Trademark Office.

As this response is filed on or before January 12, 2006, Applicants believe that no fee is due. However please charge any fee that may be due to Deposit Account Number 503344, Ref. No. 37737-003.

Amendments to the Specification are found on page 2.

Amendments to the Claims begin on page 3.

Remarks begin on page 32.

Certificate of Deposit Under 37 C.F.R. § 1.10

Pursuant to 37 C.F.R. §1.10, I hereby certify that the attached Amendment and Response, along with a Terminal Disclaimer, check number 30833 in the amount of $130, and a self-addressed stamped acknowledgment card, is being deposited with the United States Postal Service with sufficient postage as Express Mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

Date: December 9, 2005

Rachel Wright
Signature of person mailing paper

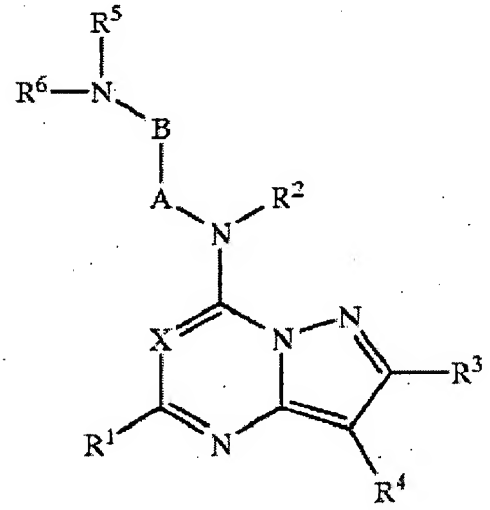
Amendments to the Specification

No amendments are made herein to the specification.

Amendments to the claims

This listing of the claims replaces all other listings of the claims pending in the present application. Please amend claim 37 as follows:

1. (previously presented) A compound of the formula:



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein:

X is CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9;

R^2 is H;

A represents an alkyl chain of 1,2, or 3 carbon atoms which is optionally mono- or di-substituted at each carbon with substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, optionally substituted at each atom with R^7;

B represents an alkyl chain of 1,2 or 3 carbons atoms, which is optionally mono- or di-substituted at each carbon with substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each of which is substituted with 1 to 5 substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is selected from:

C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C_1-C_2 haloalkyl, oxo, OR^7, cyano, NR^8R^9, $CONR^8R^9$, $COOR^7$, $SO_2NR^8R^9$, SO_2R^7, $NR^{11}COR^{12}$, $NR^{11}SO_2R^7$;

Aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl(C_5-C_8)cycloalkyl, or heteroaryl(C_5-C_8)cycloalkyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be take together to form a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

C_3-C_{10} cycloalkyl or C_2-C_9 heterocycloalkyl containing one, two, or three O, S, or N atoms, each of which is optionally substituted with 1 to 6 substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, oxo, halogen, C_1-C_6 haloalkyl, OR^7, NR^8R^9, (with the proviso that when two OR^7 or NR^8R^9 substituents are geminally located on the same carbon R^7 is not H and the geminally located OR^7 or NR^8R^9 substitutuents can be taken together to form a C_2-C_4 ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, oxo, hydroximino, C_1-C_6 alkoximino, $SO_2NR^8R^9$, SO_2R^7, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$,

$COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring; or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4- tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4- tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-(1,1-dioxo) tetrahydrothiopyranyl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octanyl, norbornyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R^7, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, CN, $COOR^7$ $SO_2NR^8R^9$, and SO_2R^7;

R^6 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl each of which is optionally substituted with 1 to 5 substituents independently from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, and SO_2R^7;

R^7 is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, and SO_2R^{13}, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or

R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each of which is optionally substituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN; and wherein

R^5 is phenyl, naphthyl, 2-,3-, or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, triazinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, isoxazolyl, indolyl, pyrazolyl, quinolyl, isoquinolyl, 2-, 4-, or 5-thiazolyl, benzothiadiazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-triazinyl, 2-pyrazinyl, 2-, or 3-furanyl, 2-, or 3-thienyl, 2-, or 3-benzothienyl, or 1-, 2- or 5-tetrazolyl each of which is optionally substituted with 1 to 5 substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein 2 adjacent substituents may be taken together to form a cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring.

2. (canceled)

3-6. (canceled)

7. (original) A compound according to claim 1, wherein;

X is CH,

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

8. (original) A compound according to claim 1, wherein:

X is CH;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

9. (original) A compound according to claim 1, wherein;

X is CH;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl;

R^4 is phenyl, mono, di, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl,

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted,

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and

R^7, R^8, and R^9 are as defined in claim 1.

10. (original) A compound according to claim 1, wherein:

X is CH;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl;

R^4 is phenyl, mono, di, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted,

R^5 is

C_1-C_6 alkyl, C_3-C_{10}cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C_1-C_2 haloalkyl, OR^7, cyano, NR^8R^9, $CONR^8R^9$, $COOR^7$, $SO_2NR^8R^9$, SO_2R^7, $NR^{11}COR^{12}$, $NR^{11}SO_2R^7$; or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4- tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4- tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-(1,1-dioxo) tetrahydrothiopyranyl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octanyl, norbornyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R^7, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, CN, $COOR^7$ $SO_2NR^8R^9$, and SO_2R^7;

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and

R^7, R^8, R^9, R^{11}, and R^{12} are as defined in claim 1.

11. (original) A method for treating eating disorders and cardiovascular disorders comprising administering to a patient suffering from an eating disorder or cardiovascular disorder a compound according to claim 1.

12. (original) A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

13-17. (canceled)

18. (original) A compound according to any one of claim I wherein in an assay of NPY binding the compound exhibits an K_i of 1 micromolar or less.

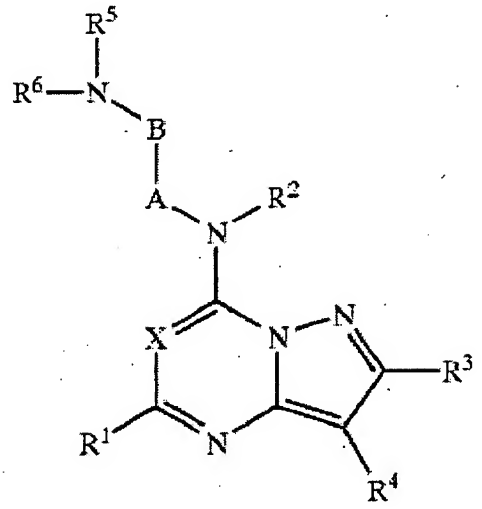
19. (original) A compound according to any one of claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 100 nanomolar or less.

20. (original) A compound according to any one of claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 100 nanomolar 10 nanomolar or less.

21. (original) A method for treating obesity or bulimia nervosa which comprises administering an effective amount of a compound according to claim 1 to a patient in need thereof.

22. (original) A method for treating hypertension which comprises administering an effective amount of a compound according to claim 1 to a patient in need thereof.

23. (previously presented) A compound in accordance with formula I



wherein:

X is CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_6 ycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9;

R^2 is H;

A is $(CH_2)_m$, where m is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, or A and B jointly form a C_3-C_6 carbocycle, optionally substituted at each occurrence with R^7;

B is $(CH_2)_n$, where n is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR7; C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

or, as mentioned above, B and A jointly form a C_3-C_6 carbocycle, optionally substituted at each occurrence with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 akynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each of which is substituted with 1 to 5 substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is selected from:

C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C_1-C_2 haloalkyl, oxo, OR^7, cyano, NR^8R^9, $CONR^8R^9$, $COOR^7$, $SO_2NR^8R^9$, SO_2R^7, $NR^{11}CO\,R^{12}$, $N\,R^{11}SO_2R^7$;

Aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl(C_5-C_8)cycloalkyl, or heteroaryl(C_5-C_8)cycloalkyl, where aryl is phenyl or naphthyl, and heteroaryl is 2-, 3- or 4-pyridyl, 2-, 4-, or 5-pyrimimidinyl, triazinyl, 1-, 2-, or 4-imidazolyl 2-, 4-, or 5-oxazolyl, isoxazolyl indolyl, pyrazolyl, quinolyl, isoquinolyl, 2-, 4-, or 5-thiazolyl, benzothiadiazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-triazinyl, 2-pyrazinyl, 2-, or 3-furanyl, 2-, or 3-thienyl, 2-, or 3-benzothienyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10}

cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluoromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR7, C_1-C_6 alkyl- NR^8R^9, $CONR^8R^9$, COOR7, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be take together to form a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

C_3-C_{10} cycloalkyl optionally substituted with 1 to 6 substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, oxo, halogen, C_1-C_6 haloalkyl, OR^7, NR^8R^9, (with the proviso that when two OR^7 or NR^8R^9 substituents are geminally located on the same carbon R^7 is not H and the geminally located OR^7 or NR^8R^9 substitutuents can be taken together to form a C_2-C_4 ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl- NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, oxo, is hydroximino, C_1-C_6 alkoximino, $SO_2NR^8R^9$, SO_2R^7, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to

form a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring; or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-(1,1-dioxo) tetrahydrothiopyranyl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octanyl, norbornyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R^7, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, CN, $COOR^7$ $SO_2NR^8R^9$, and SO_2R^7;

R^6 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6) alkyl each of which is optionally substituted with 1 to 5 substituents independently from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^3, C_1-C_6 alkyl- NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, and SO_2R^7;

R^7 is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, and SO_2 R^{13}, with the proviso that when R^7 is SO_2 R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a

C_2-C_5 aminoheterocycle each of which is optionally substituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

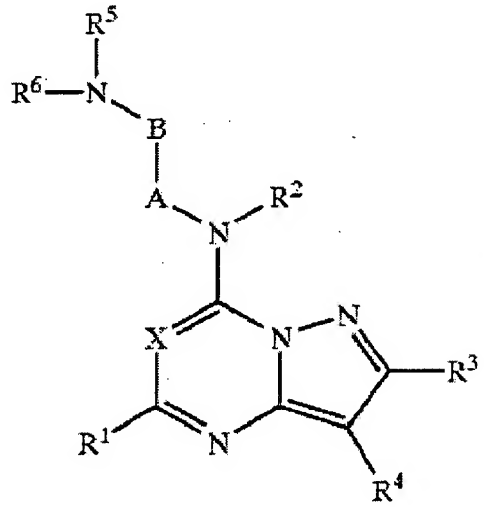
R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with O R^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN;

or a pharmaceutically acceptable salt, hydrate or prodrug thereof.

24. (previously presented) A compound in accordance with formula I



or a pharmaceutically acceptable salt, hydrate or prodrug thereof wherein:

X is CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9;

R^2 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, wherein each alkyl or cycloalkyl group may be optionally substituted with 1 to 3 R^{7a} groups;

R^2 may optionally join with R^5 and the two and the 2 nitrogen atoms to which they are bound to form a 6 to 10 membered heterocyclic ring optionally substituted at each carbon with $R^{7(a)}$;

A represents an alkyl chain of 1, 2 or 3 carbon atoms which is optionally mono- or di-substituted at each carbon with substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, or A and B jointly form a C_3-C_6 carbocycle, optionally substituted at each occurrence with R^{7a};

B represents an alkyl chain of 1,2 or 3 carbons atoms, which is optionally mono- or di-substituted at each carbon with substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR7; C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 allyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each of which is substituted with 1 to 5 substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl)- , C_2-C_4 alkynyl wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is selected from:

C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10}, cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6, alkenyl, halogen, C_1-C_6 haloalkyl, OR^7, NR^8R^9, (with the proviso that when two OR^7 or NR^8R^9substituents are geminally located on the same carbon R^7 is not H and the geminally located OR^7 or NR^8R^9 substitutuents can be taken together to form a C_2-C_4 ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl- NR^8R^9, CO NR^8R^9, $COOR^7$, CN, oxo, hydroximino, C_1-C_6 alkoximino, $SO_2NR^8R^9$, SO_2R^7, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at

each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10}, cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring; with the proviso that C_1-C_6 alkyl group is substituted with a C_1-C_6 alkyl group to give a C_7-C_{10} alkyl group

Aryl(C_1-C_6) alkyl, heteroaryl(C_1-C_6)alkyl, aryl(C_5-C_8)cycloalkyl, or heteroaryl(C_5-C_8)cycloalkyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluoromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkenyl, or a 3 to 10 membered mono- or bicyclic heterocycle containing 1-3 O, S or N atoms, each of which is optionally substituted with 1 to 6 substituents independently selected from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, OR^7, NR^8R^9, (with the proviso that when two OR^7 or NR^8R^9 substituents are geminally located on the same carbon R^7 is not H and the geminally located OR^7 or NR^8R^9 substitutuents can be taken together to form a C_2-C_4 ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, oxo, hydroximino, C_1-C_6 alkoximino, $SO_2NR^8R^9$, SO_2R^7, COR^7, heterocycloalkyl, aryl, C_1-C_6 alkylaryl, heteroaryl, C_1-C_6 alkylheteroaryl where aryl or heteroaryl is optionally substituted

with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR7, NR^8R^9, C_1-C_6 alkyl-OR7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring; or

aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethiylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, $S0_2R^7$, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl)- , wherein any 2 adjacent substituents may be taken together to form a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

R^6 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, aryl(C_1-C_6)alky- l, heteroaryl(C_1-C_6)alkyl each of which is optionally substituted with 1 to 5 substituents independently from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, and SO_2R^7;

R^7 is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl- NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, and SO_2R^{13};

R^{7a} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, and SO_2R^{13}, with the proviso that when R^{7a} is SO_2R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or $R^8$and R^9 taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each of which is optionally substituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is for SO_2 R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

25. (original) A compound according to claim 24, wherein R^{14} is H, C_1-C_4 alkyl, F or Cl.

26. (original) A compound according to claim 25, wherein

R' is H, C_1-C_4 alkyl, (C_3-C_6 cycloalkyl) C_1-C_2 alkyl, where the alkyl and cycloalkyl groups are optionally substituted with 1-3 fluorines.

R^3 is H, C_1-C_4 alkyl, (C_3-C_6 cycloalkyl) C_1-C_2 alkyl, where the alkyl and cycloalkyl groups are optionally substituted with 1-3 fluorines.

A is CH_2, optionally substituted with one or two of the following: F, CF_3, or C_1-C_3 alkyl;

B is a 1, 2 or 3 carbon chain, optionally substituted with one or two of the following: F, CF_3, or C_1-C_3 alkyl.

27. (original) A Compound according to claim 26, wherein

R^2 is H;

R^6 is H;

R^4 is phenyl, substituted with 2 or 3 substituents independently selected from C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_2-C_4 alkenyl, F, Cl, CF_3, CHF_2, CH_2CF_3, OMe, OCF_3, OEt, OPr, OiPr, C_2-C_4 alkyl OH, C_2-C_6 alkynyl, wherein the phenyl ring is minimally 2,4 di-substituted.

28. (previously presented) A Compound according to claim 27, wherein

A is CH_2;

B is CH_2;

R^{7a} is independently selected at each occurrence from H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, (C_3-C_6) C_1-C_2 alkyl, C_1-C_2 fluoroalkyl, heterocycloalkyl, C_1-C_4 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_2 arylalkyl or C_1-C_2 heteroarylalkyl each optionally substituted with 1 to 3 substituents independently selected from F, Cl, CF_3, OR^{13}, NR^8R^9, C_1-C_2 alkyl-OR^{13}, C_1-C_2 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, and CN;

R^8 is H, C_1-C_3 alkyl, CF_3 or CH_2CF_3;

R^9 is H or C_1-C_3 alkyl;

R^{13} is H, C_1-C_3 alkyl, CF_3 or $CH_2C F_3$.

29. (original) A Compound according to claim 27, wherein

A is CH_2, optionally substituted with one or two of the following: F, CF_3, or methyl, ethyl, isopropyl;

B is CH_2, optionally substituted with one or two of the following: F, CF_3, methyl, ethyl,

or Isopropyl.

30. (previously presented) A Compound according to claim 29, wherein

R^5 is C_1-C_7, alkyl, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl C_1-C_2 alkyl, substituted with F, CF_3, OR^7 or NR^8R^9;

A is CH_2, optionally substituted with methyl;

B is CH_2, optionally substituted with methyl;

X is CH.

31. (original) A compound according to claim 30, wherein

R^7 is H, C_1-C_3 alkyl, CF_3 or CH_2CF_3;

R^8 is H, C_1-C_3 alkyl, CF_3 or CH_2CF_3,

R^9 is H or C_1-C_3 alkyl or N R^8R^9 taken together to form a pyrrolidine, piperidine or morpholine ring.

32. (previously presented) A Compound according to claim 29, wherein

R^5 is 3- or 4-tetrahydropyranyl, 3-tetrahydrofluranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-cyclhexenyl, or 3-cyclopentenyl, optionally substituted with 1 or 2 substituents selected from C_1-C_3 alkyl;

A is CH_2, optionally substituted with methyl;

B is CH_2 optionally substituted with methyl; and

X is CH.

33. (original) A Compound according to claim 29, wherein

R^5 is 3- or 4-piperidinyl or 3-pyrrolidinyl, optionally substituted on 1 or 2 carbons with C_1-C_3 alkyl, and one substituent on nitrogen from H, C_1-C_6, alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, (C_3-C_6 cycloalkyl) C_1-C_2 alkyl, C_1-C_4 alkenyl, C_1-C_3 fluoroalkyl, C_2-C_4 alkyl-OR^7, C_2-C_4 alkyl-NR^8R^9, heterocycloalkyl, CO- C_1-C_4 alkyl, aryl, C_1-C_3, alkylaryl, heteroaryl, C_1-C_3 alkylheteroaryl where aryl or heteroaryl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_3 alkyl, F, Cl, C_1-C_2 fluoroalkyl, OR^7, NR^8R^9, C_1-C_2 alkyl-OR^7, C_1-C_2 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3 -, 4-, or 5 -(2-oxo-1,3-oxazolidinyl).

34. (previously presented) A Compound according to claim 33, wherein

R^5 is 3- or 4-piperidinyl or 3-pyrrolidinyl, optionally substituted on nitrogen with H, C_1-C_3 alkyl, CH_2CF_3, acetyl, pyridyl, benzyl, methylenepyridyl, pyrimidinyl, or pyrazinyl, where the aryl or heteroaryl group is optionally substituted with 1 to 2 substituents independently selected at each occurrence from C_1-C_3, alkyl, F, Cl, CF_3, OR^7, NR^8R^9;

R^7 is H, C_1-C_2, alkyl, CF_3 or CH_2CF_3;

R^8 is H, C_1-C_2 alkyl, CF_3 or CH_2CF_3;

R^9 is H or C_1-C_2 alky;

A is CH_2, optionally substituted methyl;

B is CH_2, optionally substituted with methyl;

X is CH.

35. (original) A compound according to claim 29, wherein

R^5 is C_1-C_2 arylalkyl, C_1-C_2 heteroarylalkyl, C_3-C_4 arylcycloalkyl, or C_3-C_4 heteroarylcycloalkyl, where aryl is phenyl or naphthyl, and heteroaryl is 2-, 3-, or 4-pyridyl, 2-, 4- or 5 pyrimidinyl, triazinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, isoxazolyl, indolyl, pyrazolyl, quinolyl, isoquinolyl, 2-, 4-, or 5-thiazolyl, benzothiadiazolyl, 1-, 3- or 4 pyrazolyl, 1-, 3- or 4-triazolyl, 2-triazinyl, 2-pyr, zinyl, 2-, or 3-furanyl, 2-, or 3-thienyl, 2-, or 3-benzothienyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, (C_3-C_6 cycloalkyl) C_1-C_2 alkyl, C_1-C_6 alkenyl, F, Cl, C_1-C_2 fluoroalkyl, OR^7, NR^8R^9, C_1-C_2 alkyl-OR^7, C_1-C_2 alkyl-NR^8R^9or CN.

36. (previously presented) A compound according to claim 35, wherein

R^5 is phenethyl, pyridinylethyl, or 2-tetrahydonaphthylenyl, each of which is optionally substituted with 1 to 2 substituents independently selected at each occurrence from C_1-C_2 alkyl, F, Cl, CF_3 OR^7, NR^8R^9;

R^7 is H, C_1-C_2 alkyl, CF_3 or CH_2CF_3;

R^8 is H, C_1-C_2 alkyl, CF_3 or CH_2CF_3;

R^9 is H or C_1-C_2 alkyl;

A is CH_2, optionally substituted with methyl;

B is CH_2, optionally substituted with methyl;

X is CH.

37. (currently amended) A compound according to claim ~~28~~ 1, where the structure is [3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-(6-methyl-

piperidin-2-ylmethyl)-amine.

38. (original) A compound according to claim 31, where the compound is selected from the group consisting of:

2-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-butan-1-ol;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1 ,5-a]pyrimidin-7-ylamino]-ethyl}-N'-methyl-cyclohexane-1,4-diamine;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-ethyl-cyclohexane-1,4-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(4-morpholin-4-yl-cyclohexyl)-ethane-1,2-diamine;

4-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylaminol} -cyclohexanol;

3-{2-[3-(2,6-dichloro-4-methox- y-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-pro- pane-1,2-diol;

N-{2-[3(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-isobutyl-cyclohexane-1,4-diamine;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[l 1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-isobutyl-cyclohexane-1,4-diamine;

4-{2-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-1-methyl-ethylamino}-cyclohexanol;

2-{2-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-cyclohexanol;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazo to [1,5-a]pyrimidin-7-yl]-N'-(4,4,4-trifluoro-butyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2,2,2-trifluoro-ethyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2-trifluoromethyl-cyclohexyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5 -a]pyrimidin-7-yl]-N'-(4-trifluoromethyl-cyclohexyl)-ethane 1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2,2-difluoro-ethyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-(2-fluoro-1-methyl-ethyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazoto [1,5-a]pyrimidin-7-yl]-N'-(2-fluoro-cyclohexyl)-ethane-1,2-diamine.

39. (original) A compound of claim 32, where the compound is selected from the group consisting of N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; N-[3-(2,4-dichloro-6-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydropyran -4-yl)-ethane-1,2-diamine; N-[3-(2,6-dichlork)-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydropyran-4-yl)-ethane-1,2-diamine; N1-[3-(2,6-Dichloro-phenyl)-2,5-dimethyl-pyrazo to [1,5-a]pyrimidin-7-yl]-N2&-(tetrahydropyran -4-yl)-propane-1,2-diamine; N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N-(2-methyl-tetrahydro-ftiran-3-yl)-ethane-1,2-dia- mine; N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyri- midin-7-yl]-N'-(tetrahydropyran -4-yl)-ethane-1,2-diamine; 3,5-dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino-]-pyrazolo [1,5-a]pyrimidin-3-yl}-benzonitrile; N-[3-(2,6-dichloro-4-propo- xy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyra- n-4-yl)-ethane-1,2-diamine; 2-(3,5-dichloro-4-(2,5-dimethyl-7-[2-(tetrahyd- ro-pyran-4-ylamino)-ethylamino]-pyrazolo [1,5-a]pyrimidin-3-yl} -phenyl)-propan -2-ol; N-[3-(2,6-dichloro-4-cyclopent-1-enyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(tetrahydro-pyran-4-yl)-ethane-1- ,2-diamine; N-[8-(2,6-dichloro-4-ethoxy-phenyl)-2,7-dimethyl-pyrazolo [1,5-a] [1,3,5]triazin-4-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamin- e; (3.5-dichloro-4-(2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylam- ino]-pyrazolo[1,5-a]pyrimidin-3-yl}-phenyl)-methanol; N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N-(2-methyl-tetrahydro-furan -3-yl)-ethane-1,2-diamine; N-[5-tert-butyl-3-(2,6-dichloro-4-methoxy-phen-

yl) -2-methyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-e- thane-1,2-diamine; N-[3-(2,6-dichloro-4-ethoxy-phenyl)-5-ethyl-2-methyl-py- razolo[1,5-a]pyrimidin-7-yl]-N-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; N-cyclohex-3-enyl-N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyra- zolo[1,5-a]pyrimidin-7-yl]-ethane -1,2-diamine; N-cyclohex-3-enyl-N'-[8-(2- ,6-dichloro-4-ethoxy-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-- yl]-ethane-1,2-diamine; N-cyclopent-3-enyl-N'-[3-(2,6-dichloro-4-methoxy-p- henyl)-2,5 -dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine.

40. (Previously presented) A compound of claim 34 where the structure is selected from the group consisting of

N-[3-(2,6-dichloro-phenyl)-2,5-dimethyi-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-19 piperidin-4-yl-ethane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-2,- 5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-ethyl-piperidin-3-yl)-ethane-1,2-diamine;

N-(1benzyl-pyrrolidin-3-yl)-N'-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo [1,5a]pyrimidin-7-yl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-pyrimidin-2-yl-ethane-1,2-diamine;

N-(1-benzylpiperidin-4-yl)-N'-[3 -(2,4-dichloro-6-methoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;

N-(1-benzyl-piperidin-4-yl)-N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;

N-[3(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1'-methyl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5 dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-(1-ethyl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl] -N'-(1-isopropyl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-(2,2,6,6-tetramethyl-piperidin-4-yl)-ethane-1,2- diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]- pyrimidin-7-yl]-N'-(1-ethyl-piperidin-3-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazo to [1,5-a] pyrimidin-7-yl]-N'-piperidin-4-yl-ethanel, 2-diamine;

N^2(1-Benzyl-piperidin-4-yl)-N'-[3-(2,6-dichloro-phenyl) -2,5-dimethyl-pyrazolo[1,5-ajpyrimidin-7-yl]-propane-1,2-diamine;

N-[3-(2,6-Dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyridin-3-ylmethyl-piperidin -4-yl)-ethane-1,2-diamine;

N-[3-(2,6-Dichloro-4-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin- -7-yl]-N'-(1-pyridin-4-ylmethyl-piperidin4-yl)-ethane-1,2-diamine;

3,5-Dichloro-4-12,5-dimethyl-7-[2-(1-phenyl-pyrrolidin -3-ylamino)-ethylamino]-pyrazolo[1 ,5-a]pyrimidin-3-yl]-phenol;

N-[3-(2,6-2,5dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidi- n-7-yl]-N'-(1-pyridin -2-ylmethyl-piperidin-4-yl)-ethane-1,2-diamine;

3,5-dichloro-4-(2,5-dimethyl-7-[2-(1-pyrimidin-2-yl-piperidin-4-ylamino)--ethylamino]-pyrazolo [1,5-a]pyrimidin-3-yl }-benzonitrile;

N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5 a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine- ;

N-[3-(2,6dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidi- n-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-(1-benzyl-piperidin-4-yl)-N'-[3(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimet- hyl-pyrazolo 1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl-]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-5isopropyl-2-methyl-pyrazoto [1,5-a]pyrimidin-7-yl]-N-(1 -pyrimidin-2-yl-piperidin-4-yl)ethane-1,2-diamine;

N-[3-(2,4-dichloro-phenyl)-5-isopropyl-2-methyl-pyrazolo [1,5a]pyrimidin-7-yl]-N'-(1 -pyrimidin -2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N'-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]p- yrimidin-7-yl]-N^2-(1 -pyrimidin -2-yl-piperidin-4-yl)-propane-1,2-diamine;

N'-[3-(2,6-dichloro-4-methoxy-phenyl)-5isopropyl-2-methyl-pyrazoto [1,5-a]pyrimidin-7-yl]-N^2-(1-pyrimidin-2-yl-piperidin-4-yl)propane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-5-ethyl-2-methylpyrazoto [1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2-methyl-5-propyl-pyrazolo[1,- 5-a]pyrimidin-7-yl]-N^2-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;

N'-[3-(2,6-dichloro-4methoxy-phenyl)-5-ethyl-2-methyl-pyrazoto [1,5-a]pyrimidin-7-yl]-N^2-(1-pyrimidin-2-ylpiperidin-4-yl)-propane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-2-methyl-5-propylpyrazoto [1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N'-[3-(2,6-dichloro-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimid- in-7-yl]-N^2-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;

N'-[3-(2,6-dichloro-phenyl)-5-ethyl 2-methyl-pyrazolo[-1,5-a]pyrimidin-7-yl]-N^2-(1-pyrimidin-2-yl-piperidin-4-yl)-propanel,2-diamine;

N-[5-ethyl-2-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N'-[5-ethyl-2-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N^2-(1-pyrimidin-2-yl-piperidin -4-yl)-propane-1,2-diamine;

N-[3-(2,6dichloro-4-ethynyl-phenyl)-2,5-dimethylpyrazolo [1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[2-methyl-5 -propyl-3 -(2,4,6-trimethyl-phenyl)-pyrazo to [1,5-a]pyrimidin-7-yl]-N'-(1 pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-(-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N'-[3-(2,6-Dimethyl-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidi- n-7-yl]-N'-(1 -pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;

N-[3 -(2,6-dimethyl-phenyl) -2-methyl-5-propyl-pyrazolo [1,5 -a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane -1,2-diamine;

N'-[3-(2,6-Dimethyl-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-- a]pyrimidin-7-yl]-NZ-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;

N'-[3-(2,6dimethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N- .sup.2-(1-pyrimidin-2-ylpiperidin-4-yl)-propane-1,2-diamine;

N-[3-(2,4-dimethyl-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl-]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,4-dimethyl-phenyl)-2-methyl-5-propyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine; and

1-[4-(1{[3-(2,6-dichloro-4-methoxyphenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-ylamino]-methyl] -propylamino)piperidin-1-yl]-ethanone.

41. (original) A compound of claim 37 where the structure is selected from the group consisting of

N-[2,5 -dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-[2-(4-methoxy-phenyl)-ethyl]-ethane-1,2diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidi- n-7-yl]-N'-[2-(4-methoxy-phenyl)-ethyl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidi- n-7-yl]-N'-[2-(3-ethoxy-4-methoxy-phenyl)-ethyl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidi- n-7-yl]-N'-[2-(4-ethoxy-3-methoxy-phenyl)-ethyl]ethane-1,2-diamine;

N-[3-(2- ,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,a]pyrimid in-7-yl]-N'-(1,2,3,4-tetrahydro-naphthalen-2-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidi- n-7-yl]-N'-(2-pyridin-2-yl-ethyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidi- n-7-yl]-N'-(2-pyridin-3-yl-ethyl)-ethane-1,2-diamine; and

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-(2-pyridin4-yl-ethyl)-ethane-1,2-diamine.

42-44. (canceled)

45. (original) A pharmaceutical composition which comprises a therapeutically effective amount of compound of claim 24 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

46. (original) A pharmaceutical composition for the treatment of obesity which comprises a therapeutically effective amount of compound of claim 24 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

47-50. (canceled)

51. (original) A pharmaceutical composition according to claim 24 for the treatment of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dislipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disorders, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.

52-79. (canceled)

Remarks

In response to the Office Action mailed October 12, 2005 from the United States Patent and Trademark Office, claim 37 is herein amended. Support for this amendment is found in claims as originally filed. No new matter is added by the present amendment.

Claims 1, 7-12, 18-36, 38-41, 45, 46, and 51 are original or previously presented and remain pending in the present Amendment and Response. Applicants reserve the right to prosecute claims having the scope of claims as originally filed in this application, or in another application having the same priority date.

Rejection for non-statutory double patenting

The Office Action on pp. 3-4 ¶1 rejects claims 18-20, 24-27, 29-36, 40, 45, 46, and 51 under the judicially created doctrine of double patenting in view of U.S. patent number 6,372,743 (" '743"). The Office Action on p. 4 ¶2 rejects claims 1, 7-12, 18-41, 45, 46, and 51 under the judicially created doctrine of double patenting in view of U.S. patent number 6,476,038 ("038").

The Office Action on p. 2 states that "a timely filed Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground ...." Accordingly, Applicants provide here a Terminal Disclaimer for the co-owned issued patents having the following respective U.S. patent numbers: 6,372,743 and 6,476,038.

Applicants assert that upon entry of the Terminal Disclaimer attached hereto that provisional rejections under the judicially created doctrine of double patenting can properly be withdrawn, an action which is respectfully requested.

Claim 37 as amended satisfies 35 U.S.C. §112 ¶2

The Office Action on pp. 4-5 ¶3 rejects claim 37 under 35 U.S.C. §112 ¶2 as lacking antecedent basis because this claim depends on claim 28. The Examiner asserts that the claim is directed to piperidin-2-ylmethyl, which requires B and R^5 to form a ring, and that claim 28 recites B as a —CH_2—.

As a preliminary matter, applicants assert that the formation of the piperidin-2-ylmethyl of claim 37 is alternatively formed by joining B and R^6.

Further, applicants herein amend claim 37 to depend directly from claim 1. Support for this amendment is found in claims 1 and 37 as originally filed. Claim 1 refers to B as an alkyl chain of 1, 2 or 3 carbons atoms, and provides that B and R^6 can jointly form a C_3-C_6 aminocarbocycle. This amendment does not change the scope of claim 37. Thus this rejection can be withdrawn, an action which is respectfully requested.

Summary

On the basis of the foregoing amendments and reasons, Applicants respectfully submit that the pending claims are in condition for allowance, which is respectfully requested.

If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicants' representative at the telephone number provided.

Respectfully submitted,

LAWSON & WEITZEN, LLP

Sonia K. Guterman

Sonia K. Guterman, Reg. No. 44,729
Attorney for Applicants
Lawson & Weitzen, LLP
88 Black Falcon Ave., Suite 345
Boston, Massachusetts 02210-2481
Tel: (617) 439-4990
Fax: (617) 439-3987
Customer Number 48425

Dated: December 9, 2005

LAWSON & WEITZEN, LLP

VENDOR: 906202 Director of the United States Patent

DATE PAID: 12/08/05

30833

VOUCHER NO.	DESCRIPTION	DATE	INVOICE NO.	AMOUNT
64777	patent filing fee Terminal Disclaimer	12/08/05	37737-003	130.00
			CHECK AMOUNT	130.00

30833

ORIGINAL DOCUMENT PRINTED ON CHEMICAL REACTIVE PAPER WITH MICROPRINTED BORDER SEE REVERSE SIDE FOR COMPLETE SECURITY FEATURES

LAWSON & WEITZEN, LLP
88 BLACK FALCON AVENUE, SUITE 345
BOSTON, MA 02210

Sovereign
5-7515/0110

NUMBER 30833

ONE HUNDRED THIRTY DOLLARS & ZERO CENTS

DATE
12/08/05

AMOUNT
$130.00

PAY
TO THE
ORDER
OF

Director of the United States Patent
and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

MP

SAFEGUARD SECURE

THIS DOCUMENT CONTAINS HEAT SENSITIVE INK TOUCH OR PRESS HERE RED IMAGE DISAPPEARS WITH HEAT

⑈030833⑈ ⑆011075150⑆ 612000154531⑈

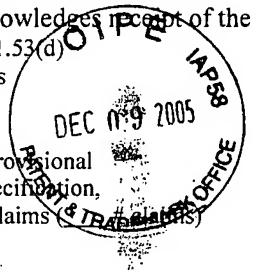
Appendix **B**

Serial No. 10/083,245 File No. 37737-003 By: S. Guterman

Title: Certain alkylene diamine-substituted pyrazolo...

Application of Darrow et al. Filing Date: Feb. 25, 2002

The U.S. PTO Mail Room acknowledges receipt of the following on the date stamped hereon:



[ ] Req. for CPA under 37 CFR 1.53(d)
[ ] Change of Attorney's Address
[ ] New Power of Attorney
[ ] Patent Application
[ ] Non-provisional [ ] Provisional
Incl. ____ pgs., (pgs.) Specification,
(pg.) Abstract, (pgs.) Claims (sheets)
[ ] Design Patent Application
[ ] Declaration(s)_____
[ ] Drawings _____ sheet(s) (Figs. ____ - ____)
[ ] Formal [ ] Informal
[X] Express Mail Label No. EQ 331866615 US
[ ] Assignment and Cover Sheet
[X] Other Terminal Disclaimer

[ ] Patent Application Transmittal Form
[ ] Inf. Discl. Statement, PTO Form SB/08
[ ] References Cited
[ ] Copy of Notice to File Missing Parts
[X] Amendment & Response
[ ] Petition for Ext. of Time (x2)
[ ] Issue Fee Transmittal
[ ] Letter to Official Draftsperson
[ ] Notice of Appeal
[ ] Brief (x3)
[X] Check for $ 130 Check # 30833
[ ] Request for Continued Examination

[ ] Transmittal Letter
[X] Cert. of Mailing under 37 CFR 1.10

DATE MAILED: December 9, 2005

Appendix C

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination
	10/083,245	DARROW ET AL.

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 01/04/06	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
Dorethea Lawrence

Appendix **D**

10/083,245
Facsimile No.: 571-273-8300
Date of Facsimile: January 31, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Darrow et al.	Docket No.:	37737-003
Serial Number:	10/083,245	Examiner:	Truong, T.
Filing Date:	February 25, 2002	Art Unit:	1625
Title:	Certain alkylene diamine-substituted pyrazolo[1,5-A]-1,3,5-triazines		

Examiner Tamthom Truong
United States Patent and Trademark Office
Art Unit 1625

Facsimile transmission of specification mark-up

1. Applicants thank the Examiner for helpful comments in telephonic interviews of January 19, 2006 and January 20, 2006.

2. Applicants here fax the Examiner the cover sheet of application having serial number 10/083,245, published as US 2003/0069246 A1, and pages of this specification that Applicants believe contain errors introduced during the publication process.

3. Applicants thank the Examiner for any assistance in correcting these errors. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicants' representative at the telephone number provided.

Respectfully submitted,

LAWSON & WEITZEN, LLP

Sonia K. Guterman

Sonia K. Guterman, Reg. No. 44,729
Attorney for Applicants
Lawson & Weitzen, LLP
88 Black Falcon Ave., Suite 345
Boston, Massachusetts 02210-2481
Tel: (617) 439-4990
Fax: (617) 439-3987
Customer Number 48425

Dated: January 21, 2006

US 2003/0069246A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2003/0069246 A1

Darrow et al. (43) Pub. Date: Apr. 10, 2003

(54) CERTAIN ALKYLENE DIAMINE-SUBSTITUTED PYRAZOLO[1,5,-A]-1,5-PYRIMIDINES AND PYRAZOLO [1,5-A]-1,3,5-TRIAZINES

(75) Inventors: **James W. Darrow**, Wallingford, CT (US); **Stephane J. De Lombaert**, Madison, CT (US); **Charles A. Blum**, Westbrook, CT (US); **Jennifer N. Tran**, Guilford, CT (US); **Mark A. Giangiordano**, Branford, CT (US); **David Andrew Griffith**, Old Saybrook, CT (US); **Philip Albert Carpino**, Groton, CT (US)

Correspondence Address:
LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023 (US)

(73) Assignee: **Neurogen Corporation**, Branford, CT (US)

(21) Appl. No.: **10/083,245**

(22) Filed: **Feb. 25, 2002**

Related U.S. Application Data

(63) Continuation of application No. 09/676,970, filed on Sep. 29, 2000, now Pat. No. 6,372,743.

(60) Provisional application No. 60/156,869, filed on Sep. 30, 1999.

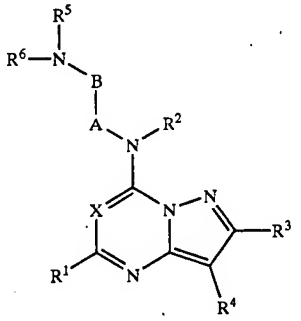
Publication Classification

(51) **Int. Cl.**[7] **A61K 31/53**; A61K 31/519; C07D 487/02

(52) **U.S. Cl.** **514/245**; 514/259.3; 544/180; 544/281

(57) **ABSTRACT**

Disclosed are compounds of the formula:



where R^1, R^2, R^3, R^4, R^5, R^6, and X are defined herein. These compounds are selective modulators of NPY1 receptors. These compounds are useful in the treatment of a number of CNS disorders, metabolic disorders, and peripheral disorders, particularly eating disorders and hypertension. Methods of treatment of such disorders and well as packaged pharmaceutical compositions are also provided.

Compounds of the invention are also useful as probes for the localization of NPY1 receptors and as standards in assays for NPY1 receptor binding. Methods of using the compounds in receptor localization studies are given.

add 2 super script

[0010] R is H,

[0011] C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each optionally substituted at each occurrence with R^7,

[0012] C_3-C_{10} cycloalkyl, or

[0013] (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

Super script

[0014] or R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted at each occurrence with R^7;

[0015] A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9,

[0016] or A and B jointly form a C_3-C_6 carbocycle, optionally substituted at each occurrence with R^7,

[0017] or, as mentioned above, A and R^2 jointly form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle optionally substituted at each occurrence with R^7;

[0018] B is $(CH_2)_n$ where n is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, or, as mentioned above, B and A jointly form a C_3-C_6 carbocycle, optionally substituted at each occurrence with R^7

[0019] or, as mentioned above, B and R^2 jointly form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle optionally substituted at each occurrence with R^7;

delete

[0020] R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9;

[0021] R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

[0022] R^5 is selected from:

[0023] C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C_1-C_2 haloalkyl, OR^7, cyano, NR^8R^9, $CONR^8R^9$, $COOR^7$, $SO_2NR^8R^9$, SO_2R^7, $NR^{11}COR^2$,$NR^{11}SO_2R^7$;

[0024] C_1-C_6 arylalkyl, C_1-C_6 heteroarylalkyl, C_5-C_8 arylcycloalkyl, or C_5-C_8 heteroarylcycloalkyl, where aryl is phenyl or naphthyl, and heteroaryl is 2-,3-, or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, triazinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, isoxazolyl, indolyl, pyrazolyl, quinolyl, isoquinolyl, 2-, 4-, or 5-thiazolyl, benzothiadiazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-triazinyl, 2-pyrazinyl, 2-, or 3-furanyl, 2-, or 3-thienyl, 2-, or 3-benzothienyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

8 super script

[0025] C_3-C_{10} cycloalkyl substituted with 1 to 6 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, OR^7, NR^8R^9, with the proviso that when two OR^7 or NR^8R^9 substituents are geminally located on the same carbon R^7 is not H and they can form together a C_2-C_4 ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, oxo, hydroximino, C_1-C_6 alkoximino, $SO_2NR^8R^9$, SO_2R^7, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

[0026] aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2

adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring; or

[0027] 3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4- tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4- tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-(1,1-dioxo) tetrahydrothiopyranyl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octanyl, norbornyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R^7, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, CN, $COOR^7$ $SO_2NR^8R^9$, SO_2R^7;

[0028] R^6 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_1-C_6 arylalkyl, C_1-C_6 heteroarylalkyl where aryl or heteroaryl are optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, or R^6 and R^2, as mentioned above, jointly form, with the 2 nitrogen atoms to which they are bound, a C_2-C_5 aminoheterocycle optionally substituted at each occurrence with R^7;

[0029] R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,

[0030] or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^{13}, R^{13} cannot be H;

[0031] R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

[0032] R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

[0033] R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

[0034] R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H;

[0035] R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN;

[0036] or a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

[0037] Preferred compounds of the present invention are those of formula I where X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

[0038] This invention also encompasses, in additional embodiments, the novel compounds of formula I, and the salts and solvates thereof, as well as pharmaceutical formulations comprising a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers, excipients, or diluents therefor.

[0039] This invention also encompasses methods to treat physiological disorders associated with an excess of neuropeptide Y, such as eating and cardiovascular disorders, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of the formula I.

[0040] This invention also encompasses methods of selectively inhibiting binding of NPY_1 receptor s, which comprises contacting a compound of formula I with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to inhibit binding of NPY_1 receptors in vitro.

DETAILED DESCRIPTION OF THE INVENTION

[0041] The current invention concerns the discovery that a select group of aminoalkyl substituted 4-amino pyrazolopyrimidines and 7-amino pyrazolo triazines, those of formula I, which are novel and useful neuropeptide Y receptor antagonists.

[0042] In certain situations, the compounds of formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

[0043] Representative compounds of the present invention, which are encompassed by formula I, include, but are not limited to the compounds in Examples 1-306 and their pharmaceutically acceptable acid addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the

free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

[0044] Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC—$(CH_2)_n$—COOH where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

[0045] The present invention also encompasses the acylated prodrugs of the compounds of formula I. "Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula I in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of the invention are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of formula I; and the like. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by formula I.

[0046] Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers. The invention includes all tautomeric forms of a compound.

[0047] By "heteroatom" in the present invention is meant oxygen or sulfur, or a nitrogen atom optionally substituted by C_1-C_6 lower alkyl, C_1-C_6 arylalkyl, C_1-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_8 alkanoyl, C_1-C_6 sulfonyl.

[0048] By "alkyl", "lower alkyl", or "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

[0049] By "cycloalkyl", or "C_3-C_{10} cycloalkyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi-, or polycyclic ring system, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

[0050] By "(cycloalkyl)alkyl", "lower (cycloalkyl)alkyl", or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl in the present invention is meant a straight or branched alkyl substituent formed of 1 to 6 carbon atoms attached to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, and the like.

[0051] The term "C_2-C_6 alkenyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or branched arrangement and containing one or more unsaturated carbon-carbon double bonds which may occur in any stable point along the chain, such as, for example, ethenyl, allyl, isopropenyl, and the like.

[0052] By "cycloalkenyl" or "C_3-C_{10} cycloalkenyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi, or polycyclic ring system having 3-10 carbon atoms and containing one or more carbon-carbon double bonds which may occur in any stable point in the ring, such as, for example, cyclopentenyl, cyclohexenyl, or cycloheptenyl.

[0053] The term "C_2-C_6 alkynyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or branched arrangement and containing one or more unsaturated carbon-carbon triple bonds which may occur in any stable point along the chain, such as, for example, ethynyl, propargyl, and the like.

[0054] The term "aryl" in the present invention means a monocyclic or bicyclic aromatic group having preferably 6 to 10 carbon atoms, such as, for example, phenyl or naphthyl.

[0055] The term "heteroaryl" in the present invention means an aryl group in which one or more of the ring(s) carbon atoms have been replaced with a heteroatom. Such groups preferably have 4 to 10 carbon atoms and 1 to 4 heteroatoms, such as, for example, pyridyl, pyrimidinyl, triazinyl, imidazolyl, oxazolyl, isoxazolyl, indolyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, thiazolyl, benzothiadiazolyl, triazolyl, triazinyl, pyrazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, tetrazolyl.

[0056] The term "heterocyclyl", "heterocycle" or "heterocycloalkyl" in the present invention means a saturated or partially saturated heteroaryl group.

[0057] By "C_1-C_6 arylalkyl" or "C_1-C_6 heteroarylalkyl" in the present invention is meant a branched or straight-chain alkyl group having 1-6 carbon atoms and substituted on one of the carbon atoms by an optionally substituted aryl or heteroaryl ring, such as, for example, benzyl, phenethyl, methylpyridyl, ethylpyridyl, and the like.

[0058] By "C_5-C_8 arylcycloalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms and fused to an aryl group, such as, for example, 1,2,3,4 tetrahydronaphthalenyl, 2,3-dihydrobenzothienyl, or 2,3-dihydobenzofuranyl.

[0059] By "C_5-C_8 heteroarylcycloalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms fused to a heteroaryl group, such as, for example, 1,2,3,4 tetrahydroquinolyl, 2,3-dihydrobenzothienyl, 2,3-dihydobenzofuranyl, or indolinyl.

[0060] By "alkoxy", "C_1-C_6 alkoxy", or "C_1-C_6 alkyloxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

[0061] By "cycloalkoxy", "C_3-C_{10} cycloalkoxy", or "C_3-C_{10} cycloalkyloxy" in the present invention is meant a group formed by an oxygen atom attached to a mono-, bi, or

these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

delete

[0085] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0086] The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0087] Compounds of general formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[0088] Dosage levels of the order of from about 0.1 mg to about 50 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 3 g per patient per day), although higher amounts for example up to 140 mg/kg/day may be appropriate in some circumstances. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

[0089] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

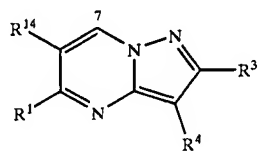
[0090] In appropriate cases, the compounds of the invention may be employed in combination with other active agents. The invention therefore also provides pharmaceutical combination compositions comprising a therapeutically effective amount of a composition comprising: (a) first compound, said first compound being a compound of the type descibed above a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a gonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent. Combinations may, for example comprise (a) first compound, said first compound being a compound as described above a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, insulin metformin, acarbose, a thiazolidinedione, a glitazone, rezulin, trogitalazone, a sulfonylurea, glipazide, glyburide, or chlorpropamide; (c) a pharmaceutical carrier, vehicle, or diluent. In other cases, a kit may be appropriate comprising: (a) first compound, said first compound being a compound of claim 24 or 25, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being a P3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; and (c) means for containing said first and second unit dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

replace w β_3

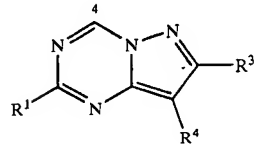
[0091] Preparation of Aminoalkyl Substituted Pyrazolo[1,5,-al-1,5-Pyrimidines and Pyrazolor[1,5-a]-1,3,5-Triazines Derivatives

[0092] One general approach is to convert a heterocyclic core A and or a heterocyclic core B

A

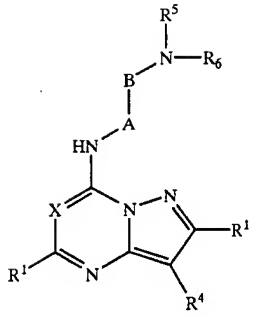


B



[0093] to a compound that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, wherein the

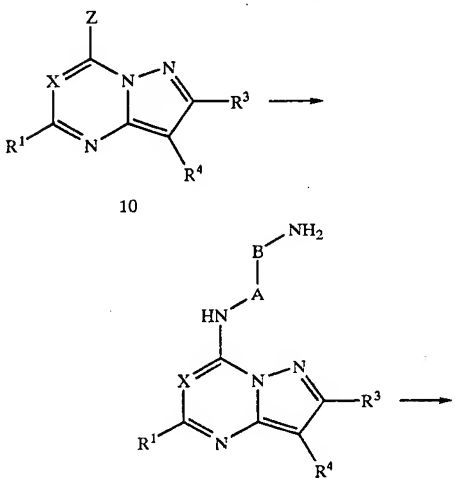
-continued



I

[0097] Alternatively, as shown in Scheme 2, compounds of formula I can be obtained by first reacting a compound of formula 10 with an amino alcohol of formula H_2N—A—B—OH, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from −78° C. to 250° C. to generate intermediates of formula 11. Reacting a compound of formula 11 with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from −78° C. to 250° C. to afford products of formula 12a (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy) or 12b when A and B are both CH_2 and X is CR^{14}. Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, PBr_5., CCl_4/PPh_3. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from −20° C. to 100° C. Compounds of formula 12a or 12b can then be reacted with an amine of formula HN[R^6]—R^5, where R^5 and R^6 are defined as above, to give a compound of formula I. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Preferred reaction temperatures range from 0° C. to 140° C.

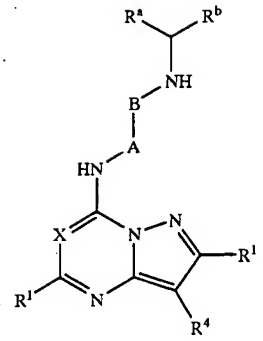
SCHEME 3



10

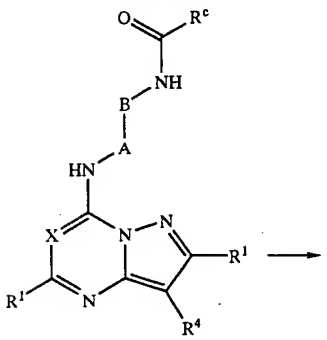
13

-continued

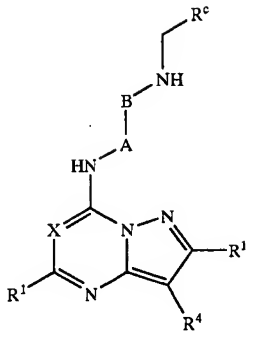


Ia

-continued



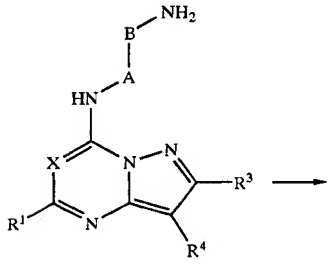
14



Ib

[0098] A subset of compounds of formula I, described under formula Ia in Scheme 3, can be obtained by first reacting a compound of formula 10 with a diamine of formula $H_2N—A—B—NH_2$, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from −78° C. to 250° C. to generate intermediates of formula 13. Reaction of a compound of formula 13 with a ketone of Formula $R^a—C=O—R^c$ or an aldehyde of Formula $R^a—C=O—R^b$ where R^b=H, in the presence of a reducing agent provides a compound of formula Ia, where the grouping $R^a—CH—R^b$ corresponds to R^5 in formula I, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethylethylamine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from −78° C. to 100° C.

SCHEME 4

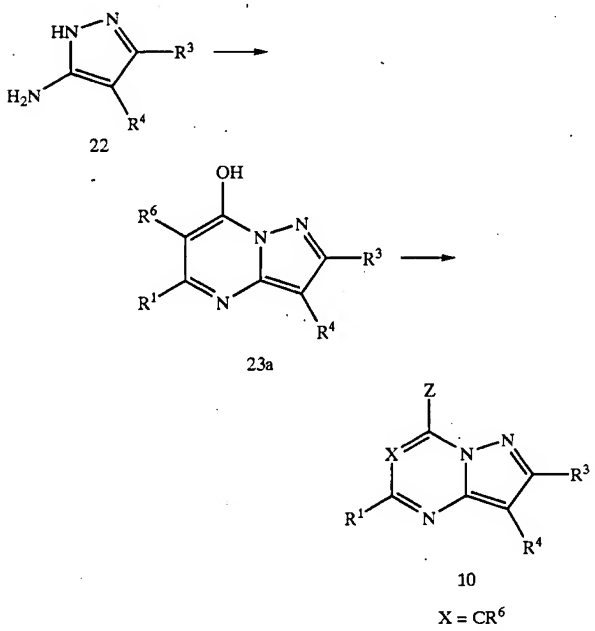


13

[0099] Alternatively, as illustrated in Scheme 4, a subset of compounds of formula I, described under formula Ib, can be obtained by first reacting a compound of formula 13 with an activated acid of formula $R^c—C=O—Z$, where Z is halo (preferably chloro), O-acyl (preferably $O—C=O—R^c$), in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from −78° C. to 250° C. to generate an amide intermediate of formula 14. Reaction of a compound of formula 14 with a reducing agent provides a compound of formula Ib, where the grouping $R^c—CH_2$ corresponds to R^5 in formula I, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethylethylamine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from −78° C. to 100° C.

minum hydride), dialkyl aluminum hydrides (such as diisobutyl aluminum hydride), alane (preferably complexed with dimethylethylamine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 6



22

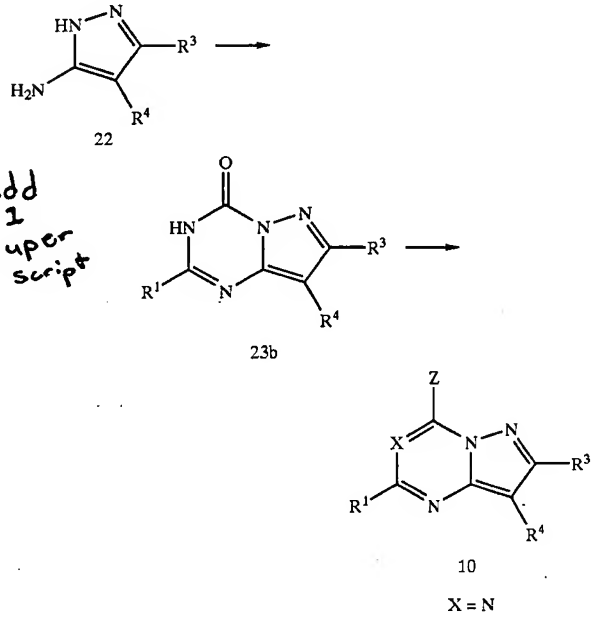
23a

10

X = CR^6

[0101] When X is CR^{14}, as defined above, compounds of formula 10 may be obtained from compounds of formula 22, as shown in Scheme 6. Compounds of formula 22 can be reacted with compounds of formula R—C═O—$CH(R^{14})$C═O—R^c, where R^1 and R^{14} are defined above, and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base in an inert solvent at reaction temperatures ranging from −50° C. to 250° C. to afford compounds of formula 23a. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Compounds of formula 23a can then be reacted with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from −78° C. to 250° C. to afford products of formula 10 (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is CR^{14}). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from −20° C. to 100° C.

SCHEME 7



22

23b

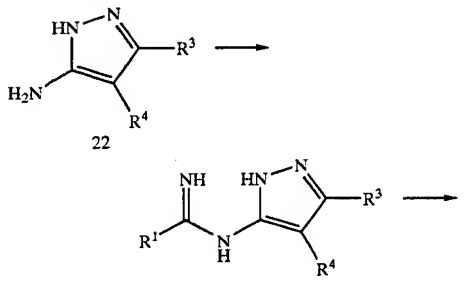
10

X = N

[0102] As shown in Scheme 7, when X is N, compounds of formula 22 can be reacted with compounds of formula R—C═N(COOR^g)—OR^f, where R^1 is defined above, and R^g is lower alkyl (1-6 carbons), and R^f is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base in an inert solvent at reaction temperatures ranging from −50° C. to 250° C. to afford compounds of formula 23b. Bases may

include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), heteroaromatic hydrocarbons (preferably pyridine). Compounds of formula 23b can then be reacted with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from −78° C. to 250° C. to afford products of formula 10 (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is N). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from −20° C. to 100° C.

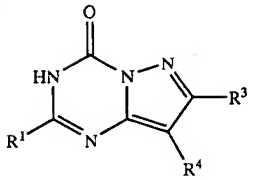
SCHEME 8



22

24

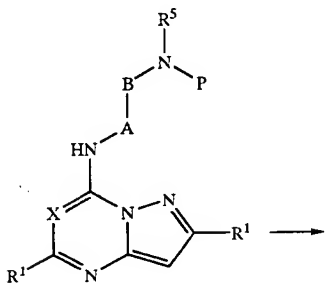
-continued



23b

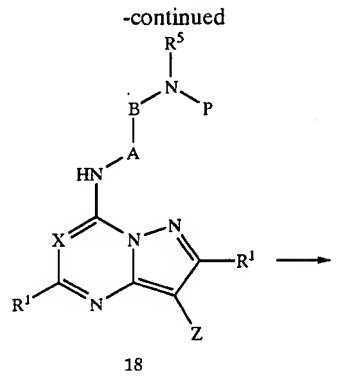
[0103] Alternatively, as illustrated in Scheme 8, compounds of formula 23b can be obtained by first reacting compounds of formula 22 with compounds of the formula R^1—(C═NH)—OR^h, where R^1 is defined above and R^h is a lower alkyl group (preferably methyl or ethyl), in the presence or absence of an acid in an inert solvent to give an intermediate of formula 24. Compounds of formula 24 react with a compound of formula R^i—C═O—R^j, where R^i and R^j are each or independently lower alkoxy (preferably methoxy or ethoxy), 1-imidazolyl, halo, aryloxy (preferably 4-nitrophenoxy) in the presence or absence of an inert solvent to afford compounds of formula 23b. Bases may include, but are not limited to, alkali metals (preferably sodium), alkali metal hydrides (preferably sodium hydride). alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 9

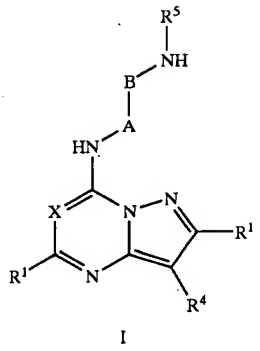


17

-continued



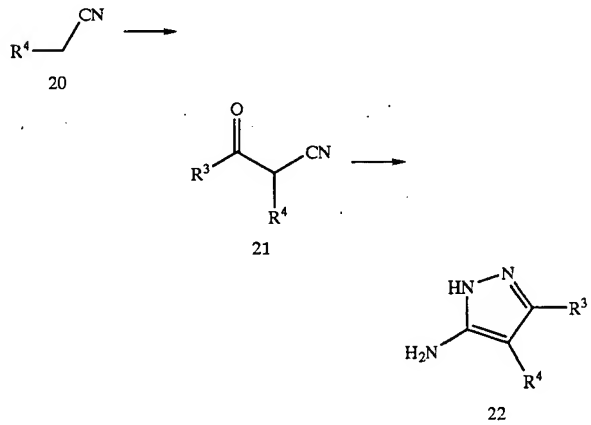
18



I

N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofliran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides(preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 10



20

21

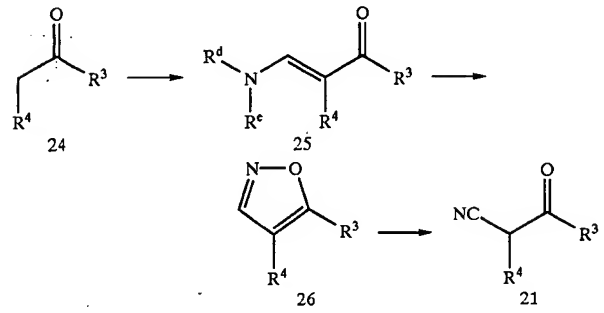
22

[0104] According to Scheme 9, compounds of formula I can also be prepared from compounds of formula 17 (prepared using the methods applicable to the synthesis of compounds of formula I), where P is H or an appropriate amino protecting group. Such groups, known in the art of organic synthesis for the protection of amines, include those listed in "Protective Groups in Organic Synthesis", by Greene and Wuts [John Wiley & Sons, NY, 1991]. Examples of amine protecting groups include, but are not limited to, acyl types (such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl), carbamate types (such as benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenymethyloxycarbonyl, allyloxycarbonyl, and 2,2,2-trichloroethyloxycarbonyl), alkyl types (such as benzyl and triphenylmethyl). Reacting compounds of formula 17 with a halogenating agent provides compounds of formula 18 where X is Br, Cl, or I. Compounds of formula 18 react with a compound of formula R^4M (where M is alkali metal, ZnCl, ZnBr, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$, copper halides, $B(OH)_2$, B(O-lower alkyl)$_2$, or Sn(lower alkyl)$_3$) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvent at temperatures ranging from −100° C. to 200° C. to give compounds of formula I (or their N-protected forms which can then be deprotected). Similar conditions have been described in WO 98/54093. Those skilled in the art will recognize that the reagents R^4M may be generated in situ. Organometallic catalysts include but are not limited to, palladium phosphine complexes (such as $Pd(PPh_3)_4$), palladium halides or alkanoates (such as $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$), or nickel complexes (such as $NiCl_2(PPh_3)_2$). Bases may include, but are not limited to, alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkali metal carbonates or bicarbonates, alkali metal hydroxides, alkali metal phosphates, or trialkylamines (preferably

[0105] As shown in Scheme 10, compounds of formula 22 may be obtained from compounds of formula 20, where R^4 is defined as above. Compounds of formula 20 are reacted with compounds of formula R^3—C═OR^c, where R^3 is defined above and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from −78° C. to 200° C. to afford compounds of formula 21. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Alternatively, compounds of formula 20 may be reacted with a solvent of formula R^3—C═O—R^c, where R^3 is defined above and R^c is lower alkoxy (1-6 carbons), in the presence of an alkali metal (preferably sodium) at reaction temperatures ranging from

-78° C. to 200° C. to afford compounds of formula 21. Compounds of formula 21 may be reacted with hydrazine (hydrate or hydrochloride salt) in an inert solvent, at reaction temperatures ranging from 0°C. to 200° C., preferably 70° C. to 150° C., to afford compounds of formula 22. Inert solvents may include, but are not limited to, water, lower alkanoic acids (preferably formic, acetic, or trifluoro acetic acid), alkyl alcohols (1-8 carbons) (preferably methanol or ethanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 11



[0106] Alternatively, compounds of formula 21 can be obtained, as illustrated in Scheme 11, by first reacting compounds of formula 24 with dialkyl formamide dialkyl acetal of formula $(R^dR^e)N—CH(OR^f)_2$ where R^d, R^e, and R^f are each or independently C_1-C_6 lower alkyl (preferably methyl) in the presence or absence of an inert solvent at reaction temperatures ranging from 0° C. to 250° C., preferably between 70° C. and 150° C. to provide compounds of formula 25. Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Compounds of formula 25 can be reacted with hydroxylamine salt (preferably hydrochloride) in the presence or absence of an inert solvent at reaction temperatures ranging from 0° C. to 250° C., preferably between 70° C. and 200° C. to provide oxazoles of formula 26. Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Oxazole intermediates of formula 26 can be reacted with a base in the presence or absence of an inert solvent at reaction temperatures ranging from 0° C. to 200° C. Bases may include, but are not limited to, alkali hydroxides (preferably sodium or potassium hydroxide), alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl fornamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

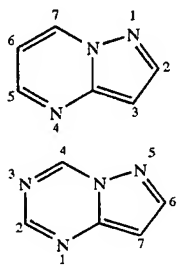
EXAMPLES

[0107] The following examples are provided to describe the invention in further details. These examples, which set forth the best mode presently contemplated for carrying the invention, are intended to illustrate and not to limit the invention.

[0108] Commercial reagents were used without further purification. THF refers to tetrahydrofuran. LDA refers to lithium diisopropylamide and DBU refers to 1,8-diazabicyclo[5.4.0]undec-7-ene. Room or ambient temperature refers to 20° C. to 25° C. Concentration implies the use of a rotary evaporator. TLC refers to thin layer chromatography. Mass spectral data were obtained either by CI or APCI methods. Other ommonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, Bu is butyl, iBu is isobutyl (CH_2-$CHMe_2$), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, cHex is cyclohexyl, Py is pyridyl, MeOH means methanol, EtOH means ethanol, EtOAc means ethyl acetate, Et_2O means diethyl ether, CH_2Cl_2 means methylene chloride, DMSO means dimethyl sulfoxide, NMP means N-methyl pyrrolidone, THF means tetrahydrofuran, DMF means dimethyl formamide, EX means example.

capitalize

[0109] The numbering system used to describe the compounds of the present invention is as follows:



Example 1

Preparation of 7-(2-(perhydro-2H-pyran-4-ylamino) ethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine

Formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R3 is CH_3, R^4 is 2,6-dimethyl-4chlorophenyl, R^5 is perhydro-2H-pyran-4-yl

[0110] A. 4-Bromo-3,5-dimethyl chlorobenzene

[0111] Slurry 2,6-dimethyl-4chloroaniline hydrochloride (23g, 193.11 g/mol) in CH_2Cl_2 (100 ml) and wash with saturated $NaHCO_3$ to generate the free base. Dry over Na_2SO_4, filter and evaporate down to a violet oil. Slurry up in 120 mL 6.0 N H_2SO_4 and stir vigorously at ambient temperature to break up larger pieces of solid. Cool to 0° C. in an ice/water bath, then portionwise over 15 minutes add a clear colorless solution of $NaNO_2$ in 50 mL H_2O. Maintain temperature 15° C. over course of addition, stirring under dry N_2. After 1 hour, carefully pour the cold reaction solution (solution A) into a second solution (solution B) containing 31.7 g CuBr in 33 mL aqueous HBr (48%) at ambient temperature. Let stand at ambient temperature until gas evolution ceases, then heat to 110° C. under N_2 while stirring. Stir for 3 hours, then cool to rt. Extract the aqueous layer with a (2:1) mixture of hexanes and Et_2O (2×500 mL), then dry the combined organic layers over Na_2SO_4, filter and evaporate down to a brown oil. Triturate the oil with hexanes (100 mL), filter out the remaining solids and wash with copious amounts of hexanes. Evaporate the hexane layers to concentrate then flush through a pad of silica to remove baseline material, using hexanes as eluent. Evaporate to a clear colorless oil (13.5g).

[0112] B. 4-Chloro-2,6-dimethyl benzaldehyde

[0113] Dissolve 4-bromo-3,5-dimethyl chlorobenzene (6.5 g) in 50 mL anhydrous THF and cool to -78° C. (dry ice/acetone) under N_2. Dropwise over 5 minutes add a solution of butyllithium (12.50 mL, 2.5M in hexanes) to the stirring solution of aryl bromide at −78° C. After 2 hours, dropwise add anhydrous DMF (5.0 mL) to the orange/red reaction solution and allow to warm to ambient temperature overnight while stirring under N_2. Evaporate the yellow solution down to a yellow oil and partition between H_2O (100 mL) and CH_2Cl_2 (100 mL). Extract the aqueous layer once with CH_2Cl_2, then pool the organic layers and dry over Na_2SO_4, filter and evaporate down to 5.0 g of yellow oil. Use without further purification. LCMS=169.6 (MEN)

Change to MH+

[0114] C. 4-Chloro-2,6-dimethyl benzyl alcohol

[0115] Dissolve 4-chloro-2,6-dimethyl benzaldehyde (5.0 g, 168.64 g/mol) in 100 mL dry methanol. Cool to 0° C. while stirring under N_2. Portionwise add powdered $NaBH_4$ (0.76g, 37.85 g/mol) over 5 minutes. Stir at 0° C. for 2 hours, monitoring by TLC until aldehyde consumed, then evaporate to a yellow oil. Add H_2O (50 mL) and bring to pH 7.0 by addition of saturated NH_4Cl. Extract the neutral aqueous layer with CH_2Cl_2 (3×75 mL) and dry the pooled organic layers over Na_2SO_4. Filter and concentrate to a yellow oil. Flush through a pad of silica to remove baseline material, then evaporate to a yellow solid (3.0 g) which can be used without further purification. LCMS=171.6 (MH^+), 169.6 (M^-).

[0116] D. 4-Chloro-2,6-dimethyl phenyl acetonitrile

[0117] Dissolve 4-chloro-2,6-dimethyl benzyl alcohol (2.8g, 170.66 g/mol) in CH_2Cl_2 (25 mL) and cool to 0° C. under N_2. Dropwise add thionyl chloride (2.4 mL, 3.90 g, 118.9 g/mol) in 10 mL CH_2Cl_2 while stirring under N_2. After 2 hours, monitoring by TLC (alcohol Rf=0.35, chloride Rf=1.0; using 20% EtOAc/80% hexanes as eluent), quench the reaction carefully by addition of saturated $NaHCO_3$ (100 mL) and stir until gas evolution ceases. Separate layers, then extract the aqueous layer with CH_2Cl_2 (100 mL). Pool the organic layers, dry over Na_2SO_4, filter and evaporate to a pale yellow oil. Take up in DMSO (25 mL), add solid NaCN (1.25 g, 49.011 g/mol) and heat to 60° C. while stirring under N_2. Stir 2 hours until chloride consumed (TLC; chloride Rf=1.0, nitrile Rf=0.6; using 20% EtOAc/80% hexanes as eluent), then cool to rt. Add 2.0 N NaOH (150 mL) and stir until orange precipitate forms, then filter and wash solid with H_2O. Dissolve solid in CH_2Cl_2, wash with H_2O, the dry over Na_2SO_4. Filter the organic layer and evaporate to an orange oil which crystallizes upon standing at rt. (2.3 g). LCMS= 180.2 (MH^+), 178.2 (M^-).

[0118] E. 2-(4-Chloro-2,6-dimethylphenyl)-3-oxobutanenitrile

[0119] Dissolve 4-chloro-2,6-dimethyl phenyl acetonitrile (2.3 g, 179.2 g/mol) in 15 mL EtOAc and add sodium metal (0.35 g, pea-sized fragments). Heat to reflux (90° C. bath temperature) under N_2 overnight. Evaporate down to solid and slurry up in Et_2O (100 mL); stir vigorously to break up fragments. Filter and wash solid with copious amounts of Et_2O. Dissolve solid in H_2O to form a clear yellow solution, and add 1.0 N HCl (100 mL) to pH 1. Extract the resulting cloudy solution with CH_2Cl_2 (3×100 mL) until aqueous layer is clear. Pool and dry the organic layers over Na_2SO_4, filter and evaporate to yellow oil (1.8g). TLC: Rf=0.2 using 20% EtOAc/80% hexanes as eluent. LCMS=222.3 (MH^+); 220.2 (M^-).

[0120] F. 5-Amino-4-(4-chloro-2,6-dimethylphenyl)-3-methylpyrazole

[0121] Dissolve anhydrous hydrazine (0.91g, 0.90 mL) in 20 mL toluene. Add glacial acetic acid (2.25 mL) and allow to stand at ambient temperature for 10 minutes until solution becomes cloudy white. Add a solution of 2-(4-chloro-2,6-dimethylphenyl)-3-oxobutanenitrile in 10 mL toluene, rinsing out the ketonitrile flask with an additional 5 mL toluene. Heat to reflux under N_2 (130° C.) with Dean-Stark trap attached. Water will begin to accumulate after 10 minutes or so. After 2 hours, evaporate down and partition between 1.0 N NaOH (100 mL) and EtOAc (100 mL). Extract aqueous layer with EtOAc (2×100 mL), then pool the organic layers and dry over Na_2SO_4. Filter and evaporate to yellow oil (1.75 g). Use without further purification. LCMS=236.5 (MH^+); 234.5 (M^-).

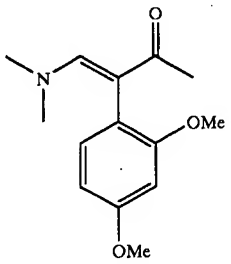
211.94 g/mol). To the resultant slurry, add glacial acetic acid (0.032 mL, 5.4×10^{-4} mol) and stir at ambient temperature under N_2 for 3 hours. Partition between CH_2Cl_2 (3 mL) and 1.0 N NaOH (10 mL), then separate the layers and chromatograph the CH_2Cl_2 layer using [10% (2.0M NH_3 in MeOH)/90% CH_2Cl_2] as eluent. Obtained 0.16 g white solid-foam upon evaporation. TLC: Rf=0.65. LCMS=422.5 (MH^+); 420.5 (M^-). H-NMR ($CDCl_3$): 6.67 (s, 2H); 5.79 (d, 1H, J=8.8 Hz); 3.98 (br. d, 2H, J=12 Hz); 3.78 (s, 3H); 3.52 (t, 2H, J=6 Hz); 3.39 (br. t, 2H, J=12 Hz); 3.37 (s, 1H); 3.04 (t, 2H, J=6 Hz); 2.75-2.81 (m, 2H); 2.40 (s, 3H); 2.18 (s, 3H); 2.00 (s, 6H); 1.89 (br. d, 2H, J=12 Hz); 1.47-1.53 (m, 2H).

Example 2

Preparation of 7-(2-(2-(4-ethoxy-3-methoxyphenyl) ethylamino)ethylamino)-3-(2,4-dimethoxyphenyl)-2, 5-dimethyl-pyrazolo[1,5-a]pyrimidine

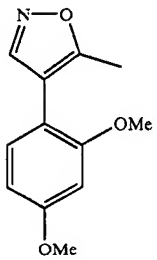
Formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,4-dimethoxyphenyl, R^5 is 2-(4-ethoxy-3-methoxyphenyl)ethylamino)ethyl

[0130] A. (3E)-3-(2,4-dimethoxyphenyl)-4-(dimethylamino)but-3-en-2-one



[0131] Dissolve 1-(2,4-dimethoxyphenyl)acetone (1.0 g, 5.15 mmol, 194.23 g/mol) in DMF-diethyl acetal (4.5 mL, 25.7 mmol, 147.22 g/mol) and stir under N_2 at 100° C. overnight. TLC using 20% EtOAc/80% hexanes; (ketone Rf=0.25, product Rf=0.0). Evaporate to thick oil, dissolve in EtOAc (25 mL) and wash with H_2O (3×25 mL). Extract pooled H_2O layers with EtOAc. Dry pooled organic layers over Na_2SO_4, filter and evaporate to thick oil which solidifies upon standing at ambient temperature (0.98 g). Use without further purification. LCMS=250.2 (MH^+); 248.2 (M^-).

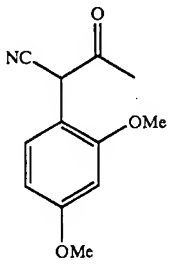
[0132] B. 4-(2,4-Dimethoxyphenyl)-5-methyl-isoxazole



[0133] Dissolve (3E)-3-(2,4-dimethoxyphenyl)-4-(dimethylamino)but-3-en-2-one (5.1 g, 20.6 mmol) in EtOH (50 mL) and add $NH_2OH.HCl$ (3.05 g, 44.0 mmol). Heat to reflux under N_2 for 20 minutes. Cool and evaporate to red-brown oil. Dissolve in CH_2Cl_2, dry over Na_2SO_4, filter and concentrate to red-brown oil (4.4 g). Use without further purification. LCMS=220.2 (MH^+); 218.2 (M^-).

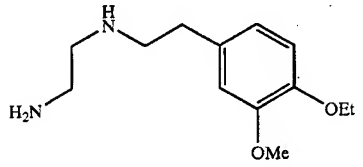
change to $NH_2OH\cdot HCl$

[0134] C. 2-(2,4-Dimethoxyphenyl)-3-oxobutanenitrile.



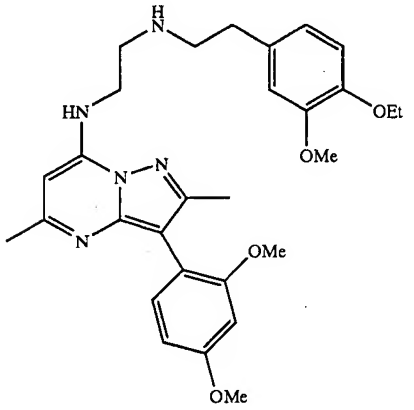
[0135] Slurry 4-(2,4-dimethoxyphenyl)-5-methyl-isoxazole (4.4 g) in 1.0 N NaOH (35 nmL) and add 35 mL MeOH to dissolve. Heat at 60° C. under N_2 for 1 hour, then cool to clear brown solution. Add 1.0 N HCl to acidify to pH 1, then filter the resulting white solid precipitate. Dissolve solid in EtOAc, dry over Na_2SO_4, filter and concentrate to red oil. Use without further purification. LCMS=220.2 (MH^+); 218.2 (M^-).

[0136] D. N-(4-Ethoxy-3-methoxy-phenethyl)-ethylenediamine.



[0137] Dissolve 4-ethoxy-3-methoxy-phenyl acetic acid (26 g, 119 mol) in dichloroethane (300 mL, anhydrous) and cool to 0° C. Dropwise add oxalyl chloride (130 mL, 2.0 M in CH_2Cl_2) and DMF (2 mL), then allow to warm to ambient temperature overnight. Evaporate down and chase with CH_2Cl_2, then evaporate to a tan oil. Dissolve in 200 mL dichloroethane and cool to 0° C. while stirring under N_2. Dropwise, over 45 minutes, add a second solution of N-tBOC-ethylenediamine (20 g) and triethylamine (20 mL) in 100 mL dichloroethane. Partition between CH_2Cl_2 (500 mL) and 1.0 N HCl (200 mL), then separate the layers and wash the organic layer with 1.0 N HCl (200 mL). Wash the organic layer with saturated K_2CO_3 (2 x 200 mL), then dry the CH_2Cl_2 layer over Na_2SO_4, filter and evaporate to tan solid. Triturate with 200 mL Et_2O and stir vigorously to fragment solid, then filter and wash copiously with Et_2O to obtain 20.5 g white solid. Dissolve white solid (3.0 g, 8.52 mmol) in 10 mL (1:1 trifluoracetic acid:CH_2Cl_2) and stir at ambient temperature 1 hour. Evaporate down and partition between CH_2Cl_2 (25 mL) and 1.0 N NaOH (25 mL), then separate the layers and extract the aqueous layer with CH_2Cl_2 (25 mL). Pool the organic layers, dry over Na_2SO_4, filter and evaporate to a white solid (1.75 g).

[0138] E. 7-(2-(2-(4-ethoxy-3-methoxyphenyl)ethylamino)ethylamino)-3-(2,4-dimethoxyphenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidine.



[0139] Dissolve 7-chloro-2,5-dimethyl-3 -(2,4-dimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine (prepared from 2-(2,4-dimethoxyphenyl)-3-oxobutanenitrile according to the methods of EXAMPLE 1 F, G and H) (0.2 g, 6.31x10mol) in dichloroethane (10 mL), then add the N-(4-ethoxy-3-methoxy-phenethyl)-ethylenediamine from step D (0.10 g, 4.2×10^{-4} mol) and diisopropylethylamine (0.1 mL, 6×10^{-4} mol) and stir under N_2 at 80° C. overnight. Wash the organic layer with saturated $NaHCO_3$ (10 mL), then evaporate the organic layer down to a yellow oil. Chromatograph using [10% (2.0 M NH_3 in MeOH)/90% CH_2Cl_2] and evaporate to obtain 50 mg pale yellow solid. LCMS=520.3 (MH^+); 518.3 (M^-). H-NMR ($CDCl_3$): 7.35 (d, 1H, J=8.4 Hz); 6.71-6.8 (m, 3H); 6.56-6.61 (m, 2H); 6.47 (t, 1H, J=5.6 Hz); 5.75 (s, 1H); 4.05 (quart., 2H, J=6.8 Hz); 3.82-3.88 (m, 5H); 3.77 (s, 3H); 3.42 (quart., 2H, J=5.6 Hz); 2.97 (t, 2H, J=6 Hz); 2.90 (t, 2H, J=6 Hz); 2.76 (t, 2H, J=7.2 Hz); 2.44 (s, 3H); 2.35 (s, 3H)1.43 (t, 3H, J=6.8 Hz).

Example 3

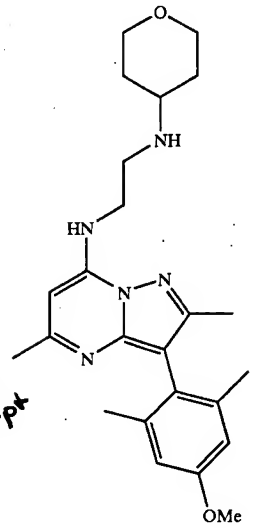
Preparation of 7-(2-(perhydro-2H-pyran-4-ylamino) ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine

Formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,4-dimethyl-4-methoxyphenyl, R^5 is perhydro-2H-pyran-4-yl

[0140] A. 4-Methoxy-2,6-dimethyl phenyl acetonitrile

[0141] Dropwise add a solution of chlorotrimethylsilane (20 mL) in CH_2Cl_2 (40 mL) to a stirred solution cooled to 0° C. of 4-methoxy-2,6-dimethyl benzyl alcohol (approx. 74 mmol) in 300 mL CH_2Cl_2. Solution changes color from colorless to yellow and then to purple over the course of the reaction. After 2 hours, monitoring by TLC (alcohol Rf=0.25, chloride Rf=0.95; using 20% EtOAc/80% hexanes as eluent), evaporate down to a yellow oil. Dissolve in dry DMF (50 mL) and cool to 0° C. under N_2. Add freshly ground NaCN (7.0 g) portionwise over 5 minute (exothermic) to the stirring reaction, forming a yellow/white slurry. Stir for 5-8 hours at 0° C. until no starting material remains, as determined by TLC (nitrile Rf=0.5; using 20% EtOAc/80% hexanes as eluent). Partition the reaction solution between EtOAc (100 mL) and 0.1 N NaOH (300 mL). Dry the EtOAc layer over Na2SO4, filter and evaporate to yellow oil. Chromatograph in 10% EtOAC/90% hexanes on silica to remove residual chloride and evaporate to 2.1 g yellow solid; clean by TLC. LCMS=176.5 (MH^+), 174.4 (M^-).

[0142] B. 7-(2-(Perhydro-2H-pyran-4-ylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine



[0143] 7-(2-(Perhydro-2H-pyran-4-ylamino)ethylamino)-2,5-dimethyl-3 -(2,6-dimethyl-4-methoxyphenyl)-pyrazolo [1,5-a] pyrimidine is obtained from 4-methoxy-2,6-dimethyl phenyl acetonitrile using the procedures described in EXAMPLE 1 E, F, G, H, I, J.

Example 4

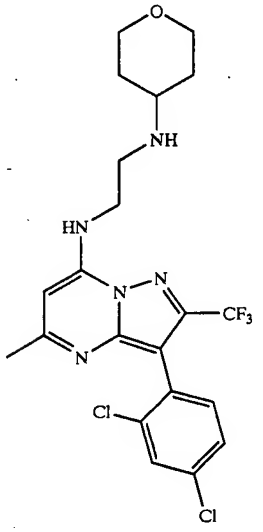
Preparation of 7-(2-(perhydro-2H-pyran-4-ylamino) ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine

Formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CF_3, R^4 is 2,4-dichlorophenyl, R^5 is perhydro-2H-pyran-4-yl

[0144] A. 2-(2,4-Dichlorophenyl)-4,4,4-trifluoro-3-oxobutanenitrile

[0145] Slurry 2,4-dichlorophenylacetonitrile (I) (5.0 g, 26.9 mmol, 186.04 g/mol) in ethyl trifluoroacetate (6.4 mL, 7.6 g, 142.08 g/mol) and add 20 mL anhydrous THF. Portionwise at ambient temperature add NaH (1.88 g, 47.1 mmol, 60% in mineral oil) over 5 minutes. Heat reaction to reflux (90° C. bath temperature) overnight. Evaporate to thick red-brown oil and partition between Et_2O (100 mL) and H_2O (60 mL). Separate layers and extract H_2O with Et_2O (2x75 mL). Acidify the aqueous layer with 1.0 N HCl to pH 1 (becomes cloudy white suspension) and extract aqueous layer with CH_2Cl_2 (3x100 mL). Dry pooled CH_2Cl_2 layers over Na_2SO_4, filter and concentrate to yellow oil (7.5 g, 26.5 mmol). Use without further purification. LCMS=281.9 (MH^+); 279.8 (M^-).

[0146] B. 7-(2-(Perhydro-2H-pyran-4-ylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine



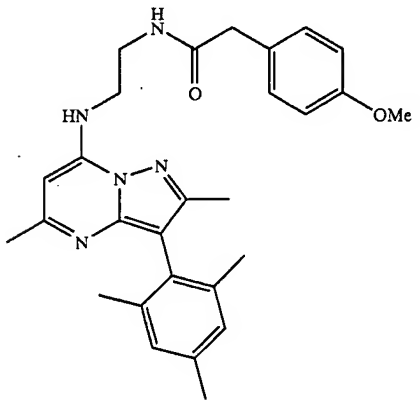
[0147] 7-(2-(Perhydro-2Hpyran-4-ylamino)ethylamino)-2-trifluoromethyl-5 -methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine is obtained from 2-(2,4-dichlorophenyl) 4,4,4-trifluoro-3-oxobutanenitrile using the procedures described in EXAMPLE 1 F, G, H, J.

Example 5

Preparation of 7-(2-(2-(4-methoxyphenyl)ethylamino)ethylamino)-3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

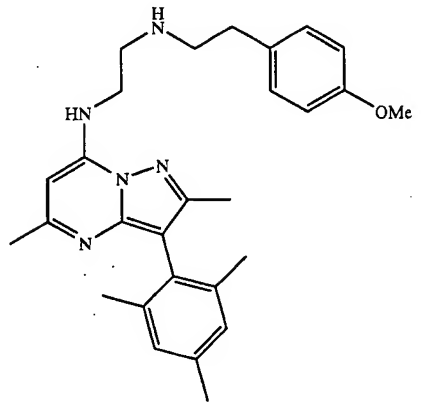
Formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,4,6-trimethylphenyl, R^5 is 2-(4-methoxyphenyl)ethylamino)ethyl

[0148] A. N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7yl)-2-(4-methoxyphenyl)acetamide



[0149] Dissolve 7-chloro-2,5-dimethyl-3 -(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine (0.26 g, 8.69×10^{-4} mol) in 2 mL N-methylpyrrolidine, and add N-(2-aminoethyl)-2-(4-methoxyphenyl)acetamide (0.75 g, 3.6 mmol). Heat to 80° C. overnight under N_2. Partition between EtOAc (50 mL) and H_2O (50 mL), then separate layers and wash EtOAC layer successively with 0.1 N NaOH (25 mL), H_2O (25 mL), and brine. Pool aqueous layers and extract with EtOAc (25 mL). Pool EtOAc layers, dry over Na_2SO_4, filter and concentrate to yellow oil. Chromatograph on silica gel eluting with EtOAc and evaporate to obtain 0.30 g of N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a] pyrimidin-7yl)-2-(4-methoxyphenyl)acetamide as a clear pale yellow oil. LCMS=472.3 (MH^+); 470.2 (M^-). ^{1}H-NMR ($CDCl_3$): 7.10 (d, 2H, J=10.2 Hz); 6.39 (s, 2H); 6.81 (d, 2H, J=10.2 Hz); 6.46 (t, 1H, J=6.0 Hz); 6.16 (t, 1H, J=6.0 Hz); 5.79 (s, 1H); 3.76 (s, 3H); 3.45-3.50 (mn, 6H); 2.38 (s, 3H); 2.30 (s, 3H); 2.20 (s, 3H); 2.02 (s, 6H).

[0150] B. 7-(2-(2-(4-methoxyphenyl)ethylamino)ethylamino)-3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidine



[0151] Dissolve N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin -7yl)-2-(4-methoxyphenyl)acetamide (0.15 g, 3.2×10^{-4} mol) in 5 mL anhydrous THF and stir under N_2. Add borane-dimethylsulfide complex (0.25 mL, 10.0 M in THF) and heat to reflux overnight. Quench by careful addition of MeOH until gas evolution ceases, then evaporate to oil. Add HCl in Et_2O (2 TnL, 1.0 M) and MeOH to solubilize (5 mL), then reflux 1 hour and evaporate. Dissolve in CH_2Cl_2 (20 mL) and wash with saturated $NaHCO_3$ (20 mL). Evaporate CH_2Cl_2 layer and chromatograph on silica gel eluting with EtOAc (Rf=0.15), then evaporate down to a clear oil (0.10 g). LCMS=458.3 (MH+), 456.4 (M^-). ^{1}H-NMR (CD_3Cl): 7.13 (d, 2H, J=8.8 Hz); 6.94 (s, 3H); 6.84 (d, 2H, J=8.8 Hz); 6.57 (t, 1H, J=5.6 Hz); 5.77 (s, 1H); 3.78 (s, 3H); 3.44 (quartet, 2H, J=5.6 Hz); 3.00 (t, 2H, J=6.0 Hz); 2.92 (t, 2H, J=6.8 Hz); 2.78 (t, 2H, J=6.8 Hz); 2.41 (s, 3H); 2.31 (s, 3H); 2.22 (s, 3H); 2.01 (s, 6H).

[0152] Alternatively, the reduction can be carried out as follows: dissolve N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-2-(4-methoxyphenyl)acetamide (0.15g, 3.2×10^{-4} mol) in 5 mL anhydrous THF. Add a fresh solution of alane·dimethylethylamine complex in toluene (2.25 mL, 9.6×10^{-4} mol) and heat to 50° C. overnight under dry N_2. Quench reaction by addition of solid $Na_2CO_3.10H_2O$ (0.5 g) and stir vigorously until gas evolution ceases. Filter through celite to remove solid and evapo-

change to $Na_2CO_3 \cdot 10H_2O$

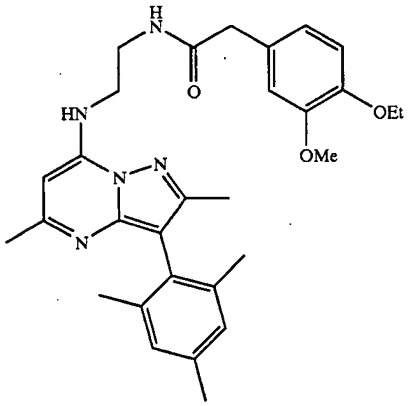
rate the filtrate down to a clear pale yellow oil. Chromatograph on silica gel eluting with EtOAc (Rf=0.15), then evaporate down to a clear oil (0.10 g).

Example 6

Preparation of 7-(2-(2-(4-ethoxy-3-methoxyphenyl) ethylamino)ethylamino)-3-(2,4,6-trimethylphenyl)-2, 5-dimethyl-pyrazolo[1,5-a]pyrimidine

Formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,4,6-trimethylphenyl, R^5 is 2-(4-ethoxy-3-methoxyphenyl)ethylamino)ethyl

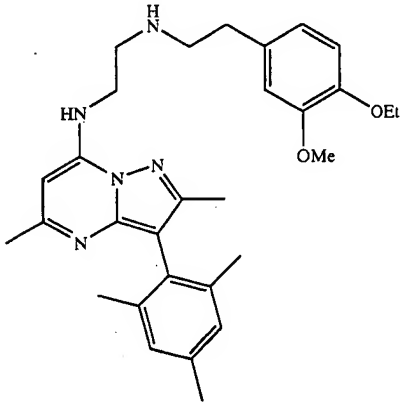
[0153] A. N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-2-(4-ethoxy-3 -methoxyphenyl)acetamide



[0154] Dissolve 7-(2-aminoethylamino)-2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a] pyrimidine (91 mg, 2.8×10^{-4} mol) in N-methyl pyrrolidine (2 mL) and add 2-(4-ethoxy-3-methoxyphenyl)acetic acid (65 mg, 3.1×10^{-4} mol). Add triethylamine (85 mg, 0.117 mL, 8.46×10^{-4} mol) and BOP-Cl (0.15 g, 3.4×10^{-4} mol), then stir at ambient temperature under N_2 overnight. Partition between H_2O (10 mL) and EtOAc (10 mL), then separate layers and wash EtOAc layer with 1.0 N NaOH (10 nmL). Dry the EtOAc layer over Na_2SO_4, filter and evaporate to oil. Use without further purification. LCMS=516.3 (MH^+); 514.2 (M^-).

[0155] Alternatively, N-(2-aminoethyl)-2-(4-ethoxy-3-methoxyphenyl)acetamide can be prepared as follows: dissolve 2-(4-ethoxy-3-methoxyphenyl)acetic acid in (26 g, 119 mol) in dichloroethane (300 mL, anhydrous) and cool to 0° C. Dropwise add oxalyl chloride (130 mL, 2.0 M in CH_2Cl_2) and DMF (2 mL), then allow to warm to ambient temperature overnight. Evaporate down and chase with CH_2Cl_2, then evaporate to a tan solid. Dissolve a portion of the tan solid acid chloride (80 mg, 3.5×10^{-4} mol) in N-methyl pyrrolidine (2 mL) and cool to 0° C. Add 7-(2-aminoethylamino)-2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a] pyrimidine (100 mg, 3.1×10^{-4} mol) and triethylamine (85 mg, 0.117 mL, 8.46×10^{-4} mol), then stir at ambient temperature under N_2 overnight. Partition between H_2O (10 mL) and EtOAc (10 mL), then separate layers and wash EtOAc layer with 1.0 N NaOH (10 mL). Dry the EtOAc layer over Na_2SO_4, filter and evaporate to oil. Use without further purification.

[0156] B 7-(2-(2-(4-Ethoxy-3-methoxyphenyl)ethylamino)ethylamino)-3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine.



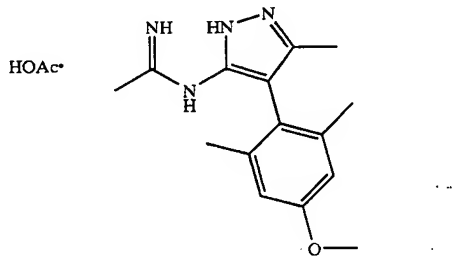
[0157] Reduction of N-(3-(2,4,6-trimethyiphenyl)-2,5-dimethyi-pyrazolo[1,5-a]pyrimidin-7-yl)-2-(4-ethoxy-3methoxyphenyl)acetaxnide with borane-dimethylsulfide complex, according, to the procedure of EXAMPLE 5, yields 7-(2-(2-(4-ethoxy-3pyrazolo[1,5-a]pyrimidine. LCMS=502.3 (MH^+); 500.4 (M^-).

Example 7

Preparation of 7-(2-(perhydro-2H-pyran-4-yiamino) ethyiamino)-2,5-dimethyi-3-(4methoxy-2,6-dimethy-iphenyi)-[1,5-a]-pyrazolo-1,3,5-triazine.

Formula I where X is N, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,6-dimethyl-4-methoxyphenyl, R^5 is perhydro-2H-pyran-4-yl

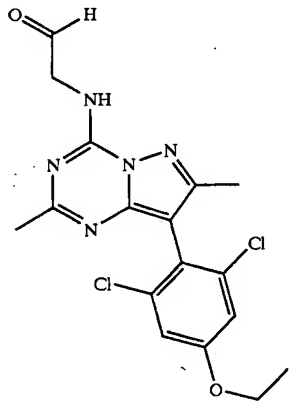
[0158] A. (Iminoethyl) [4-(4-methoxy-2,6-dimethylphenyl)-3 -methylpyrazol-5-yl]amine acetate salt.



[0159] To a solution of 5-amino-4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazole (1.89 g) (prepared from 4-methoxy-2,6-dimethyl benzaldehyde according to Example 1 C—F) in acetonitrile (30 mL) add ethylacetimidate (free base, 1.8 mL) followed by acetic acid (0.47 mL). Collect the precipitate that formed upon stirring overnight by filtration. Wash the solid with dry ether and dry to afford 2.61 g of (iminoethyl)[4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazol-5-yl]amine acetate salt as a white powder.

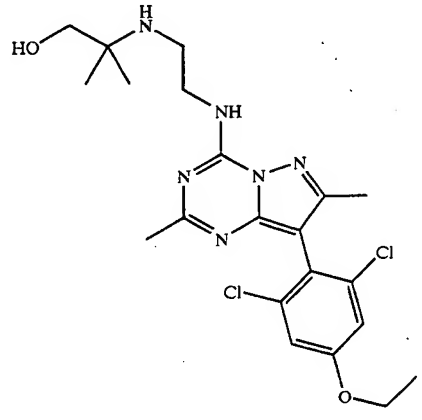
acetal. Heat the solution to 60° C. and stir under a dry nitrogen atmosphere for 2-6 hours. Remove the solvent under reduced pressure, dilute with 10% NaOH and extract with ethyl acetate. Wash the combined extracts with brine, dry over anhydrous sodium sulfate and concentrate under reduced pressure to obtain a yellow oil which crystallizes upon standing. The product, 2,6-dimethyl-7-(2,6-dichloro -4-ethoxyphenyl)-4-(2,2-dimethoxyethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine, is used without further purification. MS (M+H).

[0176] B. 2-{[7-(2,6-dichloro-4-ethoxyphenyl)-2,5,6-trimethyl-3-pyrazolino[2,3-a]1,3,5-triazin -4-yl] amino}ethanal.



[0177] Dissolve the product obtained from step D in neat trifluoroacetic acid (25 mL). After allowing the mixture to stand at ambient temperature for 0.5 h, concentrate the mixture under reduced pressure. Add saturated aqueous sodium bicarbonate and stir the resulting heterogeneous mixture for 0.5 h. Extract the aqueous solution with EtOAc, wash the EtOAc extracts with brine and then dry over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure yields the aldehyde as an off-white foam. ^{1}H NMR (CDC13): δ 9.79 (s, 1H, CHO).

[0178] F. 2-[(2-{[7-(2,6-dichloro-4-ethoxyphenyl)-2,6-dimethylpyrazolo[1,5-a]1,3,5-triazin-4-yl] amino}ethyl)amino]-2-methylpropan-1-ol.



[0179] Dissolve the aldehyde (62 mg, 0.16 mmol) obtained from step E in dry dichloroethane (4 mL). Add 1.1 equivalents of 2-amino-2-methyl-1-propanol (15 μL) followed by 1 equivalent of acetic acid. After the addition of sodium triacetoxyborohydride (1.4 eq), stir the solution at ambient temperature for several hours. Dilute the reaction mixture with 4 volumes of methylene chloride then wash the mixture with brine (1×), dry over anhydrous Na2SO4. Concentrate under reduced pressure. Preparative thin layer chromatography [10% MeOH(2N NH_3)/CH_2Cl_2)] of the oily residue yields 2-[(2-{[7-(2,6-dichloro-4-ethoxyphenyl)-2,6-dimethylpyrazolo[1,5-a]1,3,5-triazin-4-yl] amino}ethyl)amino]-2-methylpropan-1-ol.

[0180] The preparation of the compounds of the present invention by the above-mentioned methods is illustrated further by the following examples, delineated in the TABLE which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. Commonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, cPr is cyclopropyl, Bu is butyl, iBu is isobutyl (CH_2-$CHMe_2$), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, cHex is cyclohexyl, Py is pyridyl, Bn is benzyl (CH_2Ph), Ac is acetyl (CH_3—(C═O)), tBOC is tert-butyloxycarbonyl (tBuO-(C═O)). EX means example.

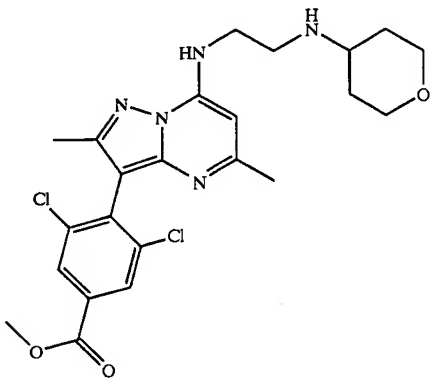
[0181] Further experimental details of the methods of Examples 119, 132, 133, 134, 277, 279, 382 and 522 are set out below.

Example 119

Preparation of 3,5-dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylaminol-pyrazolo [1,5a]pyrimidin-3-yl}-benzoic acid methyl ester

Formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,6-dichloro-4-methoxycarbonylphenyl, R^5 is tetrahydropyranyl

[0182]



[0183] A. 4-(7-{2-[tert-Butoxycarbonyl-(tetrahydro-pyran-4-yl)-amino]-ethylamino}-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-dichloro-benzoic acid methyl ester

[0184] A suspension of methanesulfonic acid 4-(7-{2-[tert-butoxycarbonyl-(tetrahydro-pyran-4-yl)-amino]-ethylamino}-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-dichloro-phenyl ester (188 mg, 0.276 nunol) from Example

step B, powdered K_3PO_4 (39 mg 0.18 mmol), and dichloro [bis(diphenylphosphino)ferrocene]palladium (60 mg, 0.085 mmol) in tetrahydrofuran (7.5 mL) was added triethylborane (1 M in THF, 2.9 mL, 2.9 mmol). The mixture was degassed with a stream of nitrogen and then stirred for 2.5 hours at 75° C. The mixture was concentrated under reduced pressure, extracted from saturated aqueous sodium bicarbonate with methylene chloride, dried (Na_2SO_4), and concentrated under reduced pressure to give crude product (1.07 g). Analysis by MS and ^1H NMR spectroscopy indicated a 1:1 mixture of product and starting material. A portion of the crude material (408 mg) was then resubjected to the above reaction conditions for 2.5 hours, then worked up as before. Chromatography (2:1 hexanes/ethyl acetate) afforded product (176 mg, 56%): +APcI MS $(M+1)^+$562; ^1H NMR (methanol-d4) δ: 7.33 (s, 2H), 6.04 (br s, 1H), 2.66 (q, 2H), 2.37 (s, 3H), 2.20 (s, 3H), 1.42 (s, 9H), 1.25 (t, 3H).

Sub Script

[0195] B. N-[3-(2,6-Dichloro-4-ethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine hydrochloride salt

[0196] To {2-[3-(2,6-dichloro-4-ethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester (0.18 g, 0.31 mmol) 2:1 ethanol/concentrated aqueous hydrochloric acid (3 mL). The reaction was stirred 15 minutes at 50° C., concentrated under reduced pressure, and then concentrated 3 additional times from ethanol to give a solid that was triturated from ether to afford the title compound (0.15 g, quantitative): +APcI MS $(M+1)^+$462; ^1H NMR (methanol-d4) δ: 7.48 (s, 2H), 6.81 (s, 1H), 2.72 (q, 2H), 2.60 (s, 3H), 2.30 (s, 3H), 1.28 (t, 3H).

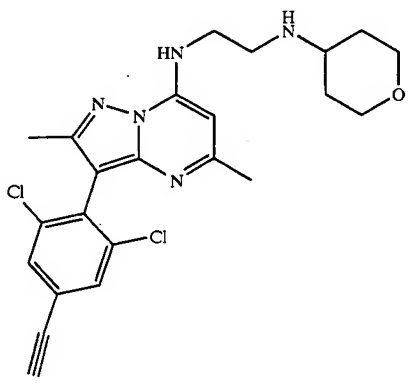
Sub Script

Example 134

Preparation of N-[3-(2,6-Dichloro-4-ethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine

Formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,6-dichloro-4-ethynylphenyl, R^5 is tetrahydropyranyl

[0197]



[0198] A. {2-[3-(2,6-Dichloro-4-hydroxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester

[0199] A stirred suspension of the crude 3,5-Dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol hydrobromide salt (8.7 mmol) from Example 382, step A in methylene chloride (100 mL) was adjusted to pH 9.5 with triethyl amine, di-tert-butyl-dicarbonate (3.0 g, 14 mmol) was added and the mixture was stirred for 2 days. The reaction then extracted from saturated aqueous sodium bicarbonate with methylene chloride, the combined organic layers were dried (Na_2SO_4) and then concentrated under reduced pressure to give the carbamate in which the phenol had been partially acylated. To a stirred solution of the residue in methanol (50 mL) was added 0.5 M sodium methoxide in methanol (30 mL, 15 mmol). After 1 hour the reaction was concentrated and then extracted from pH 7 buffer with methylene chloride. The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure and then chromatographed (10:1 ethyl acetate/methanol) to give the product (2.8 g, 58%) as a beige foam: +APcI MS $(M+1)^+$ 550; ^1H NMR ($CDCl_3$) δ: 6.70 (s, 2H), 5.84 (s, 1H), 2.51 (s, 3H), 2.24 (s, 3H), 1.54 (s, 9H).

[0200] B. Methanesulfonic acid 4-(7-{2-[tert-butoxycarbonyl-(tetrahydro-pyran-4-yl)-amino]-ethylamino}-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-dichloro-phenyl ester

[0201] To a 0° C. stirred solution of {2-[3-(2,6-Dichloro-4-hydroxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester (2.0 g, 3.6 mmol) and 2,6-lutidine (1.2 mL, 11 mmol) in methylene chloride was added trifluoromethanesulfonic anhydride, dropwise. After 15 minutes the reaction was extracted from saturated aqueous sodium bicarbonate with methylene chloride, the combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, concentrated again from toluene to remove the lutidine, and then chromatographed (2:1 to 3:1 ethyl acetate/hexanes) to give the product (1.7 g, 69%) as an off-white foam: +APcI MS $(M+1)^+$ 682; ^1H NMR ($CDCl_3$) δ: 7.37 (s, 2H), 5.84 (s, 1H), 2.45 (s, 3H), 2.25 (s, 3H), 1.53 (s, 9H).

[0202] C. {2-[3-(2,6-Dichloro-4-trimethylsilanylethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester

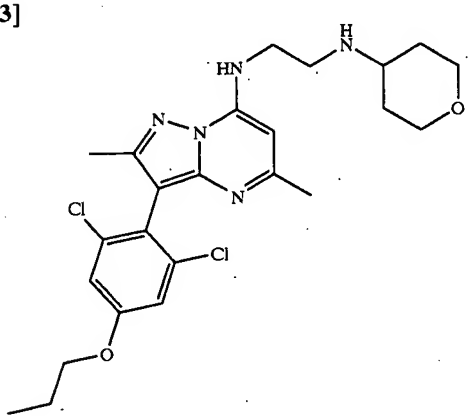
[0203] A suspension of methanesulfonic acid 4-(7-{2-[tert-butoxycarbonyl-(tetrahydro-pyran-4-yl)-amino]-ethylamino}-2,5 -dimethyl-pyrazolo[1,5 -a]pyrimidin-3-yl)-3,5 -dichlorophenyl ester (1.5 g, 2.2 mmol) in acetonitrile (5 mL)/triethylamine (1.9 mL) was degassed (3×) by alternately pulling a vacuum followed by repressurization with nitrogen. Trimethylsilylacetylene (0.50 mL, 3.6 mmol), dichlorobis(triphenylphosphine)palladium (65 mg, 0.093 mmol), and copper(I) iodide (42 mg, 0.22 mmol) were added, and the mixture was degassed (3X) again. The

Example 382

Preparation of N-[3-(2,6-dichloro-4-propoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine hydrochloride salt

Formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,6-dichloro-4-propoxyphenyl, R^5 is tetrahydropyranyl

[0223]



[0224] A. 3,5-Dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol hydrobromide salt

[0225] A suspension of N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine (4.1 g, 8.2 mmol), from Example 279, step F, in concentrated aqueous HBr (30 mL) was stirred at reflux. After 5 hours the reaction was concentrated under reduced pressure at 70° C. to give the hydrogen bromide salt as a brown oil (7.35 g). A small portion was triturated from ether to give the product as a brown solid: +APcI MS $(M+1)^+$ 450; ^{1}H NMR (methanol-d_4) δ: 7.00 (s, 2H), 6.85 (s, 1H), 4.11 (t, 2H), 4.02 (dd, 2H), 3.60-3.40 (m, 5H), 2.61 (s, 3H), 2.29 (s, 3H), 2.095 (m, 2H), 1.74 (qd, 2H).

[0226] B. N-[3-(2,6-Dichloro-4-propoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine hydrochloride salt

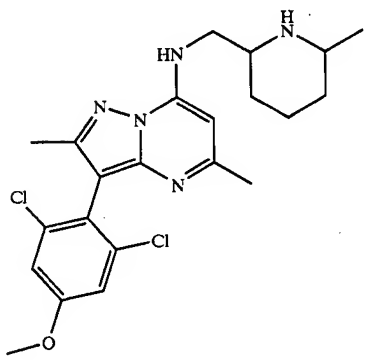
[0227] A solution of crude 3,5-Dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol hydrobromide salt (8.7 mmol) from step A in isopropyl alcohol (50 mL) was adjusted to pH 12 with 6 M aqueous NaOH. Propyl iodide (1.3 mL, 14 mmol) was added and the reaction was heated at reflux for 4 hours. The reaction was cooled and then extracted from saturated aqueous sodium bicarbonate with methylene chloride, dried (Na_2SO_4), concentrated under reduced pressure, and then chromatographed (10:1:0.1 methylene chloride/methanol/ammonium hydroxide) to give the product (2.0 g, 47%). A solution of the product in ethanol was treated with 1 M ethereal HCl (1 eq., 4.1 mmol), the mixture was concentrated to give a solid which was repulped from 1:1 ethanol/ether. The solids were collected to give the title compound (700 mg) as a colorless solid. The mother liquor was concentrated and then repulped from ether to give the remainder of the product as an off-white solid (1.3 g): +APcI MS $(M+1)^+$ 492; ^{1}H NMR (methanol-d4) δ: 7.21 (s, 2H), 6.67 (s, 1H), 2.61 (s, 3H), 2.33 (s, 3H), 1.10 (t, 3H).

Subscript

Example 522

[3-(2,6-Dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(6-methyl-piperidin-2-ylmethyl)-amine

[0228]



[0229] A. Preparation of methanesulfonic acid 6-methyl-pyridin-2-yl ester: Methanesulfonyl chloride (0.94 mL, 12.18 mimol) was added to a solution of 6-methyl-2-pyridinemethanol (1g, 8.12 mmol) and triethylamine (1.7 mL, 12.18 mmol) in THF (20 mL) at 0° C. The reaction mixture was stirred for 40 min, then was quenched with sat'd aq $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with sat'd aq NaCl, dried and concentrated in vacuo. The crude residue was chromatographed on SiO_2-gel using 50% EtOAc/hexane to give the product as an oil. ^{1}H NMR (Unity-400, $CDCl_3$): δ 7.6 (t), 7.26 (d), 7.15 (d), 5.28 (s), 3.1 (s), 2.5 (s).

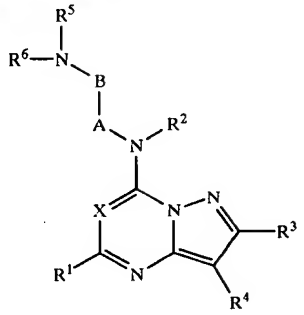
[0230] B. Preparation of 2-azidomethyl-6-methyl-pyridine: A mixture of the mesylate (1.0 g, 9.45 mmol) and sodium azide (610 mg, 9.45 mmol) in DMSO (40 mL) was stirred for 1 hr at room temperature. The reaction mixture was poured into EtOAc and was washed with sat'd aq NaCl, dried and concentrated in vacuo. The crude residue was purified using silica gel chromatography (25% EtOAc/hexanes) to give 936 mg of desired product. ^{1}H NMR (Unity-400, $CDCl_3$): δ 7.6 (t), 7.1 (d), 7.08 (d), 4.43 (s), 2.54 (s). SO

[0231] C. Preparation of (6-methyl-piperidin-2-yl)-methylamine: A mixture of the product obtained in Step B (860 mg) and PtO_2 (86 mg) in acetic acid (20 mL) was hydrogenated in a Paar Shaker at 40 psi for 17 h. The reaction mixture was filtered and the filtrate was concentrated under vacuum to give 2 g of the desired product. ^{1}H NMR (Unity-400, CD_3OD): δ 3.1, 1.93 (s), 1.88 (m), 1.55 (m), 1.28 (dd, 3 H).

[0232] D. Preparation of [3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(6-methyl-piperidin-2-ylmethyl)-amine): A solution of 7-chloro-3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidine (50 mg, 0.11 mmol), triethylamine (1 mL) and the product from step C (42 mg, 0.22 mmol) in EtOH (3 mL) was heated under reflux for 17 h. The reaction was concentrated under vacuum. The residue was diluted with sat'd aq $NaHCO_3$ and the aqueous solution was extracted with EtOAc (3×), dried and concentrated in vacuo. The crude residue was purified on a prep TLC plate using 1.5% Et_2NH/EtOAc to give 36 mg of the desired product. ^{1}H NMR (Unity-400, $CDCl_3$): δ 7.0 (s, 2H), 5.94 (s, 1H), 3.8 (s, 3H), 3.53 (m), 3.05 (m), 2.8 (m), 2.44 (s, 3H), 2.27 (s, 3H). 1.9 (m), 1.7 (m). MS 448 (M).

-continued

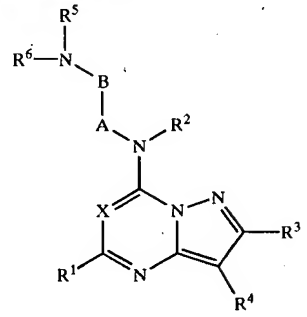
Table of Additional Examples



Ex	X	R^1	R^2	R^3	R^4	A-B-N[R^6]-R^5	MW
483.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-(1-piperidino)-cHex)	518.74
484.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-(1-pyrrolidino)-cHex)	490.68
485.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-(1-pyrrolidino)-cHex)	504.71
486.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-(NH—CH2-2-pyridyl)-cHex)	541.73
487.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-(NH—CH2-4-pyridyl)-cHex)	541.73
488.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-(NH-iBu)-cHex)	492.70
489.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-NiBu—NSO2—Me)-cHex)	570.79
490.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-(NMe—NiBu)-cHex)	506.73
491.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-ethyleneketal-cHex)	479.61
492.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-NHiBu-cHex)	506.73
493.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-NHSO2-Me-cHex)	514.68
494.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-oxo-cHex)	435.4
495.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4,4-diMe-cHex)	449.63
496.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4,4-dioxo-tetrahydrothian-yl)	471.62
497.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(tetrahydropyran-4-yl)	439.63
498.	N	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(trans-4-COOet-cHex)	494.63
499.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(trans-4-COOEt-cHex)	493.64
500.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(trans-4-COOH-cHex)	465.59
501.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-cyclohex-3-enyl	419.57
502.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-piperidin-4-yl	422.5
503.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	CH2—CHMe—NH-(1-(5-Et-pyrimidin-2-yl)-piperidin-4-yl)	542.70
504.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	CH2—CHMe—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	514.68
505.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	CH2—CMe2—NH-(1-(5-Et-pyrimidin-2-yl)-piperidin-4-yl)	556.7
506.	CH	Me	H	Me	2,6-diMe-4-tBu—Ph	(CH2)2—NH-(tetrahydropyran-4-yl)	449.64
507.	CH	Et	H	Me	2,6-diMe—Ph	(CH2)2—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	484.65
508.	CH	Et	H	Me	2,6-diMe—Ph	(CH2)2—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	484.65
509.	CH	nPr	H	Me	2,6-diMe—Ph	(CH2)2—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	498.7
510.	CH	Me	H	Me	2,6-diMe—Ph	(CH2)2—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	470.6
511.	CH	Et	H	Me	2,6-diMe—Ph	(CH2)2—NH-(1-Ac-piperidin-4-yl)	448.62
512.	CH	Et	H	Me	2,6-diMe—Ph	(CH2)2—NH-(1,2,3,4-tetrahydro-naphthalen-2-yl)	453.6

-continued

Table of Additional Examples



Ex	X	R^1	R^2	R^3	R^4	A-B-N[R^6]-R^5	MW
513.	CH	Et	H	Me	2,6-diMe—Ph	CH2—CHMe—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	498.7
514.	CH	nPr	H	Me	2,6-diMe—Ph	CH2—CHMe—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	512.7
515.	CH	Me	H	Me	2,6-diMe—Ph	CH2—CHMe—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	484.7
516.	CH	Et	H	Me	2,6-diMe—Ph	CH2—CHMe—NH-(1,2,3,4-tetrahydro-naphthalen-2-yl)	467.7
517.	CH	Me	H	Me	2,6-diOMe—Ph	(CH2)2—NH-(1-Et-piperidin-4-yl)	452.4
518.	CH	Me	H	Me	2,6-diOMe—Ph	(CH2)2—NH-(4-ethyleneketal-cHex)	481.59
519.	CH	Me	H	Me	2,6-diOMe—Ph	(CH2)2—NH-(4-oxo-cHex)	437.3
520.	CH	Me	H	Me	2,6-diOMe—Ph	(CH2)2—NH-(tetrahydropyran-4-yl)	425.52

[0233] The pharmaceutical utility of compounds of this invention are indicated by the following assays for human NPY-1 receptor activity.

[0234] Assay for Human NPY-1 Receptor Binding Activity

[0235] Compounds are assayed for activity using the following method: Baculovirus-infected Sf9 cells expressing recombinant human NPY-1 receptors are harvested at 42-48 hours at which time batches of 500 mL of cell suspension are pelleted by centrifugation. Each pellet is re-suspended in 30 mL of lysis buffer (10 mM HEPES, 250 mM sucrose, 0.5 gg/mL leupeptin, 2 μg/mL Aprotonin, 200 μM PMSF and 2.5 mM EDTA, pH 7.4) and gently homogenized by 50 strokes using a dounce homogenizer. The homogenate is centrifuged at 4° C. for 10 minutes at 536× g to pellet the nuclei. The supernatant is collected into a fresh tube and centrifuged twice in the same buffer at 48,000× g for 40 minutes. The final pellet was re-suspended in 10 mL of PBS containing 5 mM EDTA by dounce homogenization and stored in aliquots at −80° C.

[0236] Purified membranes are washed by PBS and re-suspended by gentle pipetting in binding buffer (50 mM Tris(HCl), 5 mM KCl, 120 mM NaCl, 2 mM CaC12, 1 mM MgCl2, 0.1% bovine serum albumin (BSA), pH 7.4). Membranes (5 μg) are added to siliconized (Sigmacote, Sigma) polypropylene tubes in addition to 0.050 nM [125I]NPY (porcine) for competition analysis or 0.010-0.500 nM [125I] NPY (porcine) for saturation analysis. For evaluation of guanine nucleotide effects on receptor affinity, GTP is added at a final concentration of 100 μM. Cold displacers are added at concentrations ranging from 10-12 M to 10-6 M to yield a final volume of 0.250 mL. Nonspecific binding is determined in the presence of 1 μM NPY (human) and accounts for less than 10% of total binding. Following a 2 hour incubation at room temperature, the reaction is terminated by rapid vacuum filtration. Samples are filtered over pre-soaked GF/C Whatman filters (1.0% polyethyleneimine for 2 hours) and rinsed 2 times with 5 mL cold binding buffer lacking BSA. Remaining bound radioactivity is measured by gamma counting. To estimate the Bmax, Kd and Ki, the results of binding experiments are analyzed using SigmaPlot software (Jandel). The binding affinity for the compounds of the invention, expressed as a Ki value, ranges from about 0.1 nanomolar to about 10 micromolar. The most active compounds of the invention have a Ki of less than 100 nanomolar and a binding selectivity of >100-fold relative to other G-protein coupled receptors, including NPY_5 and CRF_1 receptors.

[0237] hNPY 1-36 Induced GTPγ^{35}S Binding at Human NPY Y1 Receptors Co-Expressed With Gαi2, Gβ1l and Gγ2 in Sf9 Cells.

[0238] Agonist induced GTPγ^{35} S binding by G-protein coupled receptors (GPCR) provides a functional measure of G-protein activation. This assay has been widely used for many GPCR's and offers the possibility to distinguish agonists from antagonists and to determine potency and efficacy of agonists for a given GPCR [Thomas et al., 1995; O'Boyle and Lawler, 1995]. GTPγ^{35} S binding activity was measured using a modification of a previously described method [Wieland and Jacobs, 1994]. Log-phase Sf9 cells were co-infected with separate baculoviral stocks encoding the hNPY Y1 receptor and the G-protein subunits αi2, β1, and γ2 followed by culturing in Hink's TNM-FH insect medium supplemented Grace's with 4.1 mM L-Gln, 3.3 g/L LAH, 3.3 g/L ultrafiltered yeastolate and 10% heat-inactivated fetal bovine serum at 27° C. 72 hours post infection, a sample of cell suspension was analyzed for viability by trypan blue dye exclusion, and the remaining Sf9 cells were harvested via centrifugation (3000 rpm/10 min/4° C.). Each pellet was re-suspended in homogenization buffer (10 mM HEPES, 250 mM sucrose, 0.5 μg/ml leupeptin, 2 μg/ml Aprotonin, 200 μM PMSF and 2.5 mM EDTA, pH 7.4) and homogenized using a Polytron (setting 5 for 30 seconds). The homogenate was centrifuged at 4° C. for 10 minutes at 536× g to pellet the nuclei. The supernatant was collected into a fresh tube and centrifuged twice in the same buffer at 48,000× g for 40 minutes. The final pellet for each membrane preparation was re-suspended in DPBS containing 5 mM EDTA and stored in aliquots at −80° C. On the day of the assay, thawed membrane homogenates were re-suspended in assay buffer (50 mM Tris pH 7.0, 120 mM NaCl, 2 mM $MgCl_2$, 2 mM EGTA, 0.1% BSA, 0.1 mM bacitracin, 100 KIU/mL Aprotinin, 5 μM GDP) and added to reaction tubes at a concentration of 30 μg/reaction tube. After adding test compounds at concentrations ranging from 10^{-11}M to 10^{-5}M, reactions were initiated by the addition of both 100 pM GTPγ^{35}S and hNPY1-36 ranging in concentration from 0.001 nM to 1.0 μM (final volume of 0.250 ml). Following a 30 minute incubation at RT°, the reaction was terminated by vacuum filtration over GF/C filters (Pre-soaked in wash buffer, 0.1% BSA) with ice-cold wash buffer (50 mM Tris pH 35 7.0, 120 mM NaCl). Bound GTPγ^{35}S was determined by liquid scintillation spectrometry. Non-specific binding was defined by 10 FM GTPγ^{35}S and represented less than 5 percent of total binding. To estimate the EC_{50}, IC_{50} and K_i, the results of GTPγ^{35}S binding experiments were analyzed using SigmaPlot software (Jandel). The binding affinity for the compounds of the invention, expressed as a Ki value, ranges from about 0.1 nanomolar to about 10 micromolar. The most active compounds of the invention have a Ki of less than 100 nanomolar.

[0239] Food Deprivation Model

[0240] Subjects.

[0241] Experimentally naive and experienced male Sprague-Dawley rats (Sasco, St. Louis, Mo.) weighing 210-300g at the beginning of the experiment were used. Animals were (d)triple-housed in stainless steel hanging cages in a temperature (22 C±2) and humidity (40-70% RH) controlled animal facility with a 12:12 hour light-dark cycle. Food (Standard Rat Chow, PMI Feeds Inc., #5012) and water were available ad libitum.

delete

[0242] Apparatus.

[0243] Consumption data was collected while the animals were housed in Nalgene Metabolic cages (Model #650-0100). Each cage was comprised of subassemblies made of clear polymethlypentene (PMP), polycarbonate (PC), or stainless steel (SS). All parts disassemble for quick and accurate data collection and for cleaning. The entire cylinder- shaped plastic and SS cage rests on a SS stand and houses one animal.

[0244] The animal is contained in the round Upper Chamber (PC) assembly (12 cm high and 20 cm in diameter) and rests on a SS floor. Two subassemblies are attached to the

LAWSON & WEITZEN, LLP

Attorneys at Law
88 Black Falcon Avenue, Suite 345
Boston, MA 02111
Telephone (617) 439-4990
Telecopier (617) 439-3987

FACSIMILE TRANSMITTAL SHEET

DATE: January 31, 2006

TO: Examiner Tamthom Truong
United States Patent and Trademark Office
Art Unit 1625

FAX#: 571-273-8300

FROM: Sonia K. Guterman

RE: U.S. Patent Application No. 10/083,245
Entitled: CERTAIN ALKYLENE DIAMINE-SUBSTITUTED PYRAZOLO...
Applicants: Darrow et al.
Filed: February 25, 2002
Docket No: 37737-003

TOTAL NUMBER OF PAGES INCLUDING COVER PAGE: 24

COMMENTS OR INSTRUCTIONS:

Dear Examiner Truong:

Please see attached Remarks and marked-up pages of the Specification of the above application as published.

Sincerely,

Sonia Guterman

Sonia K. Guterman, Reg. No. 44729
Attorney for Applicants

********** -COMM. JRNAL- ********** DATE JAN-31-2006 *** TIME 15:00 *********

MODE = MEMORY TRANSMISSION START=JAN-31 14:50 END=JAN-31 15:00

FILE NO.=049

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	8	15712738300-37737003	024/024	00:09:27

-LAWSON AND WEITZEN LLP -

********** - ***** - 617 439 3987- **********

LAWSON & WEITZEN, LLP

Attorneys at Law
88 Black Falcon Avenue, Suite 345
Boston, MA 02111
Telephone (617) 439-4990
Telecopier (617) 439-3987

FACSIMILE TRANSMITTAL SHEET

DATE: January 31, 2006

TO: Examiner Tamthom Truong
United States Patent and Trademark Office
Art Unit 1625

FAX#: 571-273-8300

FROM: Sonia K. Guterman

RE: U.S. Patent Application No. 10/083,245
Entitled: CERTAIN ALKYLENE DIAMINE-SUBSTITUTED PYRAZOLO...
Applicants: Darrow et al.
Filed: February 25, 2002
Docket No: 37737-003

TOTAL NUMBER OF PAGES INCLUDING COVER PAGE: 24

COMMENTS OR INSTRUCTIONS:

Dear Examiner Truong:

Please see attached Remarks and marked-up pages of the Specification of the above application as published.

Sincerely,

Sonia Guterman

Sonia K. Guterman, Reg. No. 44729
Attorney for Applicants

Auto-Reply Facsimile Transmission

TO: Fax Sender at 617 439 3987

Fax Information
Date Received: 1/31/2006 2:49:20 PM [Eastern Standard Time]
Total Pages: 24 (including cover page)

ADVISORY: This is an automatically generated return receipt confirmation of the facsimile transmission received by the Office. Please check to make sure that the number of pages listed as received in Total Pages above matches what was intended to be sent. Applicants are advised to retain this receipt in the unlikely event that proof of this facsimile transmission is necessary. Applicants are also advised to use the certificate of facsimile transmission procedures set forth in 37 CFR 1.8(a) and (b), 37 CFR 1.6(f). Trademark Applicants, also see the Trademark Manual of Examining Procedure (TMEP) section 306 et seq.

Received Cover Page =======>

JAN-31-2006 14:50 LAWSON AND WEITZEN LLP 617 439 3987 P.01

LAWSON & WEITZEN, LLP
Attorneys at Law
88 Black Falcon Avenue, Suite 345
Boston, MA 02111
Telephone (617) 439-4990
Telecopier (617) 439-3987

FACSIMILE TRANSMITTAL SHEET

DATE: January 31, 2006

TO: Examiner Tamthom Truong
United States Patent and Trademark Office
Art Unit 1625

FAX#: 571-273-8300

FROM: Sonia K. Guterman

RE: U.S. Patent Application No. 10/083,245
Entitled: CERTAIN ALKYLENE DIAMINE-SUBSTITUTED PYRAZOLO...
Applicants: Darrow et al.
Filed: February 25, 2002
Docket No: 37737-003

TOTAL NUMBER OF PAGES INCLUDING COVER PAGE: 24

COMMENTS OR INSTRUCTIONS:

Dear Examiner Truong:

Please see attached Remarks and marked-up pages of the Specification of the above application as published.

Sincerely,
Sonia Guterman
Sonia K. Guterman, Reg. No. 44729
Attorney for Applicants

Appendix **E**

Search results as of: 11-20-2006::11:38:57 E.T.

Transaction History

Date	Transaction Description
10-20-2006	Petition Entered
10-12-2006	Petition Decision - Dismissed
07-05-2006	Petition Entered
06-28-2006	Mail Abandonment for Failure to Respond to Office Action
06-28-2006	Mail Examiner Interview Summary (PTOL - 413)
06-06-2006	Examiner Interview Summary Record (PTOL - 413)
06-24-2006	Abandonment for Failure to Respond to Office Action
06-14-2006	Case Docketed to Examiner in GAU
05-11-2006	Case Docketed to Examiner in GAU
01-31-2006	Miscellaneous Incoming Letter
01-19-2006	Paralegal TD Accepted
01-11-2006	Date Forwarded to Examiner
12-09-2005	Amendment after Final Rejection
10-12-2005	Mail Final Rejection (PTOL - 326)
09-19-2005	Final Rejection
07-12-2005	Date Forwarded to Examiner
06-30-2005	Response after Non-Final Action
04-07-2005	Mail Non-Final Rejection
04-06-2005	Non-Final Rejection
03-02-2005	Correspondence Address Change
03-02-2005	Change in Power of Attorney (May Include Associate POA)
03-02-2005	Date Forwarded to Examiner
02-14-2005	Response to Election / Restriction Filed
02-14-2005	Request for Extension of Time - Granted
12-13-2004	Mail Restriction Requirement
12-10-2004	Requirement for Restriction / Election
07-21-2004	Reference capture on IDS
07-07-2004	Information Disclosure Statement (IDS) Filed
06-28-2004	Correspondence Address Change
06-29-2004	Change in Power of Attorney (May Include Associate POA)
03-17-2004	IFW TSS Processing by Tech Center Complete
01-16-2004	Reference capture on IDS
02-25-2002	Information Disclosure Statement (IDS) Filed
05-23-2002	Preliminary Amendment
03-29-2002	Information Disclosure Statement (IDS) Filed
05-14-2002	Case Docketed to Examiner in GAU
02-25-2002	Preliminary Amendment
04-17-2002	Application Dispatched from OIPE
04-16-2002	Application Is Now Complete
04-11-2002	CRF Is Good Technically / Entered into Database
02-25-2002	CRF Disk Has Been Received by Preexam / Group / PCT
02-25-2002	Initial Exam Team nn

03-28-2002	IFW Scan & PACR Auto Security Review
03-15-2002	IFW Scan & PACR Auto Security Review
02-25-2002	Initial Exam Team nn

Close Window

Appendix **F**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Darrow et al.	Docket No.:	37737-003
Serial Number:	10/083,245	Examiner:	Truong, T.
Filing Date:	February 25, 2002	Art Unit:	1625
Title:	Certain alkylene diamine-substituted pyrazolo[1,5-A]-1,3,5-triazines		

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Terminal Disclaimer

The co-owners, Pfizer, Inc. and Neurogen Corporation, of the instant application assigned by the inventors James Darrow, Stephane De Lombaert, Charles Blum, Jennifer Tran, Mark Giangiordano, David Griffith, and Philip Carpino,

hereby disclaim, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§154 to 156 and 173, as presently shortened by any terminal disclaimer, from the date of the notice of abandonment (June 28, 2006) to the filing of this petition (May 1, 2007). This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or patent issued thereon.

The undersigned Applicant's representative files this Terminal Disclaimer under 37 C.F.R. §1.34(a). Check number 36078 in the amount of $130.00 for the terminal disclaimer fee under 37 C.F.R. § 1.20(d) is included. Applicants believe no additional fee is due,

however the Commissioner is hereby authorized to charge any additional fees or make any credits to Deposit Account No. 503344, Ref. No. 37737-003.

Respectfully submitted,

Sonia K. Guterman

Sonia K. Guterman, Reg. No. 44,729
Lawson & Weitzen, LLP
88 Black Falcon Ave., Suite 345
Boston, Massachusetts 02210-2481
Tel: (617) 439-4990
Fax: (617) 439-3987
Customer Number 48425

Date: